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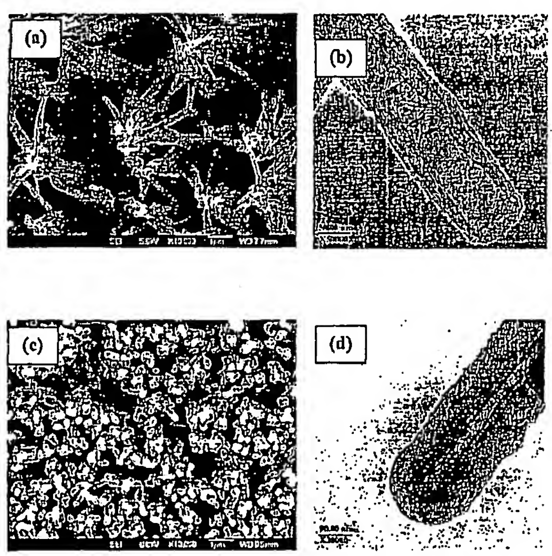

(57) Abstract: The present invention provides conductive carbon nanotube (CNT) electrode materials comprising aligned CNT substrates coated with an electrically conducting polymer, and the fabrication of electrodes for use in high performance electrical energy storage devices. In particular, the present invention provides conductive CNTs electrode material whose electrical properties render them especially suitable for use in high efficiency rechargeable batteries. The present invention also provides methods for obtaining surface modified conductive CNT electrode materials comprising an array of individual linear, aligned CNTs having a uniform surface coating of an electrically conductive polymer such as polypyrrole, and their use in electrical energy storage devices.

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COATED CARBON NANOTUBE ARRAY ELECTRODES

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

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FIELD OF THE INVENTION

The present invention relates generally to electrically conductive carbon nanotube electrode materials, methods for their preparation and their use as electrodes in high performance rechargeable batteries.

BACKGROUND OF THE INVENTION

Carbon nanotubes (CNTs) offer significant advantages over other materials in that they possess substantially higher strength-to-weight ratios and superior mechanical properties. Since their discovery, there have been numerous disclosures in the art pertaining to synthesis and morphology of CNTs, including methods for controlling tubule growth during their formation. Efforts to realize many potential applications envisaged for CNTs include their modification to produce new one-dimensional nanoscale materials, introduction of foreign materials by capillary and electric arc methods, and conversion into nanoscale carbide materials such as silicon carbide (SiC), tungsten carbide (WC), etc. by reacting them with the corresponding metal-oxides.

Electrically conductive polymers (ECPs) have been studied extensively over the past two decades. Simple ECPs, typically polypyrrole (PPy), polyaniline (PAni), polythiophene (PTh) and polyacetylenes (PA), can be prepared either chemically or electrochemically. Besides having relatively high conductivity in oxidized and ion-doped states, simple ECPs also show interesting physicochemical properties that are potentially useful in batteries, energy storage cells, sensors, capacitors, light-emitting diodes, and electrochromic displays. For many of these applications, especially in batteries, a high charge capacity is required. In order to increase the charge capacity of a polymer battery, the doping charge of the polymer film must be increased. This goal can be practically achieved by increasing the film thickness of ECPs. However, it has been found that the electrical performance of conducting polymers is strongly influenced by the

kinetics of the doping-undoping process of ions within the film. For a conventional PPy electrode, increasing the film thickness causes deterioration of electrodic performance (e.g., charging-discharging rate) due to the long ion diffusion time and migration length in the thick film. It has been shown that a porous PPy structure with large specific surface area is a prerequisite for high-power applications due to the high charging and discharging rates. Films of nitrile-butadiene rubber (NBR) when used as a template for oriented growth of PPy in NBR matrix-grown PPy electrodes possess an open, porous structure with high surface area admitting a faster anion doping process than ordinary PPy electrodes.

Methods for coating metals and organic conductive polymers on the surface of CNTs to produce one-dimensional nanoscale composites can be used in battery, magnetic storage, fuel cell, and composite applications, since they are extremely porous substrates with large surface area and possess good mechanical properties. The use of carbon substrates for improving mechanical properties of electrically conducting polymers is known. This method however, requires greater than 25% (by weight) of polypyrrole to be deposited on the fibers in order to achieve a continuos phase that is critical for electrical conductance. Efforts to use CNTs as viable substrates for electrically conducting materials disclosed in the art have been largely limited to fabrication of one-dimensional nanoscale composites of CNTs containing polypyrrole (PPy), nickel (Ni), Cobalt (Co), titanium (Ti), tungsten (W), palladium (Pd), gold (Au), aluminum (Al) and iron (Fe). Such composites, which are typically obtained by chemical synthesis, physical vapor deposition and electron-beam evaporation methods however, do not provide coating uniformity on the CNT surface, which is critical for their application in energy storage devices. This limitation is mainly attributable to tangling and isolation of randomly distributed CNTs in an array, resulting in overlapping of individual CNTs within the array and loss of coating contiguity, and therefore, causes electrical insulation between individual CNTs.

SUMMARY OF THE INVENTION

The present invention provides CNT electrode materials comprising aligned CNT substrates coated with an electrically conducting polymer and the fabrication of electrodes for use in electrical energy storage devices such as fuel cells and capicitors. In particular, the present invention provides surface modified carbon nanotube (CNTs) electrode material whose electrical properties render them suited for use in energy storage devices such as rechargeable batteries. More specifically, the present invention provides methods for obtaining surface modified CNT electrode materials comprising a CNT substrate containing a substantially

uniform surface coating of an electrically conducting polymer such as polypyrrole (PPy), wherein the CNT substrate comprises an array of individual linear CNTs are aligned with respect to one another. Linear CNTs as defined herein, refer to CNTs that do not contain branches originating from the surface of individual CNT tubules along their linear axes. The redox performance of the polymer coated CNT electrodes of the present invention is superior to conventional, flat titanium (Ti) and platinum (Pt) electrodes due to their substantially larger accessible surface area. The porosity of the electrodes of the invention, due to the hollow structure of the individual tubules within the aligned arrays, results in an especially large film formation charge (Q_{film}) that is desirable for construction of high performance rechargeable batteries. The linear CNT tubules of the present invention further comprise a substantially uniform coating of an electrically conductive polymeric material. Preferably, the coated linear CNTs are aligned in an array. The present invention further comprises methods for using the energy storage CNT electrode materials in electrical storage devices.

The electrically conducting CNT electrode material of the invention includes an aligned CNT array that is obtainable by known methods disclosed in the art. Such methods involve growing a CNT array on a metallic material containing a catalyst that is deposited on a surface. The catalyst facilitates CNT nucleation and the growth process on the metallic surface. In one embodiment, titanium (Ti) is used as a base surface upon which a nickel (Ni) layer is deposited (as the catalyst) by magnetron sputtering. Depending on the thickness of the catalytic Ni layer and growth time of CNTs, tubules having uniform lengths and similar diameters are obtainable. An electrically conducting polymeric film is subsequently deposited uniformly on the entire surface of individual tubules in the CNT array. In a preferred embodiment, the polymer film is formed in-situ and deposited on the CNT tubule surface. The in-situ synthesis and deposition of the electrically conducting polymer film can be carried out by electrochemical polymerization of the corresponding monomer from either an aqueous solvent or mixed solvents in the presence of the aligned CNT array. The polymer coatings in the electrodes of the invention are rendered adherent by pre-treatment of CNT substrates with an acidic solution prior to the coating process.

The in-situ formation of electrically conducting polymer film on CNT tubules by the methods of the present invention enables control of coating uniformity and film thickness of the electrically conducting coating polymer on individual tubules in the CNT array. The coating methods of the present invention overcome limitations of polymer solution coating methods to obtain electrically conducting polymer films on substrates. Such limitations include film non-

uniformity and variable coating thickness, which result in producing defects that produce electrically-insulating domains on the substrate surface.

The present invention further provides methods for polymerizing monomers capable of forming electrically conducting polymeric films directly on the CNT surface in their doped or undoped states. Preferably, a solution containing the monomer is contacted with the CNT array substrate, following which the monomer is electrochemically polymerized in-situ to provide a uniform polymeric coating on the surface of individual CNT tubules comprising the substrate.

In one aspect, the present invention provides a uniform film coating comprising an electrically conducting polymer, such as for example, polypyrrole (PPy) on a CNT substrate material having linear, longitudinally aligned array of tubules. The electro-deposition of conductive polymeric films on the CNT substrate material is preferably carried out in an inert atmosphere (in the absence of oxygen) to provide a surface coatings that are distributed uniformly and contiguously over the entire tubule surface. In another aspect, the CNT substrate material is pretreated with an aqueous acid, such as a mineral acid, to improve conductive polymer film adhesion to the substrate surface.

The present invention also provides methods of fabricating the conducting polymer coated CNT electrode material into electrodes that are capable of charging and discharging electrical energy, thereby enabling their use as electrodes in energy storage and dispensation devices such as rechargeable batteries. The electrical storage properties of the CNT electrodes of the present invention can be measured by standard methods such as cyclic voltammetry.

An advantage of the CNT coating methods of the present invention is that they enable the formation of highly uniform, contiguous, thin electrically conducting polymer films on a light weight mechanically strong, highly porous CNT substrate. The methods of the invention, therefore, provide electrode materials for fabrication of electrodes that are capable of superior electrical charge retention properties, enabling their use in high performance energy storage devices such as rechargeable batteries relative to conventional materials. Such devices utilizing electrodes of the present invention therefore, provide advantages of portability and fewer charge cycle requirement in comparison with devices containing conventional electrodes. The CNT electrode materials of the present invention, therefore, improve both performance and life of rechargeable batteries.

In one aspect, the present invention provides carbon nanotube (CNTs) substrates comprising uniform and contiguous electrically conducting polymer coatings that are capable of functioning as electrodes in energy storage devices.

In another aspect, the present invention provides methods for coating CNT substrates with electrically conducting materials, particularly electrically conducting polymers that are capable of functioning as electrode materials.

In another aspect, the present invention provides methods of utilizing CNT substrates coated with electrically conducting materials as electrodes in energy storage devices such as rechargeable batteries.

It is yet another aspect of the present invention to provide CNT electrodes containing electrically conducting polymers that are doped with n-type or p-type dopants for enhanced electrical conductivity.

The foregoing and other objects, features and advantages of the invention will become more apparent from the following description of the figures and detailed description of particular embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

The objects and features of the invention can be better understood with reference to the following detailed description and accompanying figures.

Figure 1 shows SEM micrographs of **(a)** an aligned CNT array substrate (D: 80nm; L: 10μm) grown on flat titanium substrate and **(b)** aligned CNT array substrate (tubule diameter: 50-70nm, length: 3-4μm) grown on a titanium substrate by plasma-enhanced chemical vapor deposition.

Figure 2 illustrates the potentiodynamic polymerization of PPy films in 0.1M $LiClO_4$ aqueous solutions. Monomer concentration (pyrrole): 17.3mM; Scan rate: 5 mV/s; Potential range: 0.0 - 0.8 V/SCE; Initial potential: 0.0 V/SCE; Substrates: aligned CNT array (a), Pt (b) and Ti (c).

Figure 3 shows SEM micrographs (3a and 3c) and the corresponding TEM micrographs (3b and 3d) images of PPy films grown on aligned CNT array substrates with different film formation charge (Q_{film}). 3a, 3b: 86.1 mC/cm^2; 3c, 3d: 1308.6 mC/cm^2.

Figure 4 shows cross-sectional SEM images of PPy films grown on the flat metal substrates: 4a Ti (645.1 mC/cm^2); 4b Pt (933.2 mC/cm^2).

Figure 5 shows SEM micrographs of free-standing conductive CNT electrode material comprised of Ppy coated aligned CNT array substrate material formed with different Q_{film}, removed from the CNT catalyst substrate: 5a 100.3 mC/cm^2; 5b 1308.6 mC/cm^2; 5c 1533.3 mC/cm^2.

Figure 6 TEM photomicrographs of Ppy coated aligned CNT array substrate with different film thickness due to different PPy film formation charge (Q_{film}): 6a 86.1 mC/cm^2; 6b 207.9 mC/cm^2; 6c 681.9 mC/cm^2; 6d 1308.6 mC/cm^2; 6e TEM image of a long PPy-coated carbon nanotube (Q_{film}: 681.9 mC/cm^2).

Figure 7 shows cyclic voltammograms of PPy films with small Q_{film} in 0.1M $LiClO_4$ monomer-free aqueous solutions. Scan rate: 100 mV/s; Potential range: -0.9 - +0.3 V/SCE; Initial potential: -0.9 V/SCE.

Figure Legends: PPy-coated aligned CNT substrate with Q_{film} = 86.1 mC/cm^2 (——); PPy films on flat Ti with Q_{film} = 93.3 mC/cm^2 (· · · · ·); and Pt with Q_{film} = 111.4 mC/cm^2 (– – – –).

Figure 8 shows cyclic voltammograms of PPy films with different Q_{film} in 0.1M $LiClO_4$ monomer-free aqueous solutions. Scan rate: 50 mV/s; Potential range: -0.9 - +0.3 V/SCE; Initial potential: -0.9V/SCE.

(8a) PPy films on flat Pt substrates, Q_{film}: 111.4 mC/cm^2 (——); 307.5 mC/cm^2 (· · · ·); 686.2 mC/cm^2 (– – – – – –); 933.2 mC/cm^2 (— · · —).

(8b) PPy films on flat Ti substrates, Q_{film}: 93.3 mC/cm^2 (——); 227.7 mC/cm^2 (· · · ·); 645.1 mC/cm^2 (– – – – – –).

(8c) PPy-coated aligned CNT substrate, Q_{film}: 86.1 mC/cm^2 (——); 207.9 mC/cm^2 (· · · · ·); 681.9 mC/cm^2 (– – – – – –); 1308.6 mC/cm^2 (— · · —).

Figure 9 shows cyclic voltammograms of the PPy films with large Q_{film} in 0.1M $LiClO_4$ monomer-free aqueous solutions. Scan rate: 25 mV/s; Potential range: -0.9 - +0.3 V/SCE; Initial potential: -0.9 V/SCE.

Figure Legends: PPy-coated aligned CNT substrate with $Q_{film} = 1308.6\ mC/cm^2$ (——); PPy films on the flat Ti with $Q_{film} = 645.1\ mC/cm^2$ (· · · · · ·) and Pt with $Q_{film} = 933.2\ mC/cm^2$ (– – – – – –).

Figure 10 shows the dependence of redox charge (Q_{redox}) of Ppy aligned CNT substrate (●), PPy/Pt (▲) and PPy/Ti (■) films on film formation charge (Q_{film}). Q_{redox} is estimated from anodic charge of the cyclic voltammogram at 50mV/s.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention relates to high surface area conductive CNT electrode materials comprising of a CNT array substrate material capable of supporting an adherent electrically conducting polymer coating. In one embodiment, the CNT electrode material comprises a porous substrate material such as, for one example a plurality of linear CNTs having a pre-determined tubule morphology. The morphology of individual tubules comprising the CNTs can be cylindrical with a hollow core, or stacked conical segments ("bamboo-like"). Alternatively, the porous substrate material can be comprised of CNT tubules having a mixture of both morphologies.

In one embodiment of the present invention, the CNT substrate material is comprised of an array of aligned linear CNTs wherein the longitudinal axis of individual tubules are oriented in a plane substantially parallel to one another.

In another embodiment, the CNT substrate material forms one or more bundles upon being coated with the conductive polymer film. A bundle as referred to herein, refers to an aggregation of a plurality of individual tubules within an array and cohesively held together by the conductive polymeric film. Thus the plurality of tubules forming a bundle are packed densely enough to produce multiple points of electrical contract between individual coated tubules, thereby establishing electrical continuity throughout the three-dimensional array of CNTs within the bundle. Alignment of the individual carbon nanotubes within a bundle is dependent on the film thickness of the electrically conductive polymer coating. In a preferred embodiment, individual CNT bundles are free standing, that is, they do not require a supporting base substrate to maintain tubule array integrity in their individual bundles.

In another aspect, the present invention provides conductive CNT electrode materials comprising porous CNT substrate materials having a substantially uniform and contiguous surface coating that is comprised of one or more electrically conductive polymers.

The CNT electrode materials of the present invention are useful in the fabrication and manufacture of electrodes for incorporation in high-efficiency energy storage devices such as rechargeable batteries, fuel cells and capacitors. In a one embodiment, the porous CNT substrate comprises an aligned array of CNTs, wherein CNT tubules within the array comprise a surface coating of at least one electrically conductive polymer. The electrically conductive polymers of the invention are known in the art, and comprise essentially polymers having an extensively π-conjugated backbones. Examples of electrically conductive polymers of the present invention include but are not limited to, for example, polypyrrole (PPy), polyaniline (PAni), polythiophene (PTh), polyacetylene (PA) and derivatives, and combinations thereof. In one embodiment, the conductive CNT electrode material comprises a plurality of electrically conductive polymers that are deposited as layered films on the surface of the CNT substrate. In a currently preferred embodiment, the electrically conductive polymer is polypyrrole (PPy).

In another aspect, the invention provides a method of producing CNT electrode materials that are free-standing (not bound to a support material) with good mechanical and electrical properties. In one embodiment, the free-standing, CNT electrode material comprises an aligned CNT substrate array coated with an electrically conductive polymer. In another embodiment, the CNT array substrate material, when subjected to the coating process of the invention, so as to provide a conductive electrical polymer film of finite thickness on the surface of individual tubules, results in "bundles" comprising an aggregate of a plurality of individual tubules. The individual tubules within each bundle are randomly aligned within a series of mutually parallel planes in a manner so as to provide a dense packing that is cohesively held together by the electrically conductive polymer coating material. This, in turn, provides multiple points of contact among individual tubules comprising the bundle, thereby establishing electrical continuity throughout the tree-dimensional array within each bundle. Individual bundles can, therefore, be rendered free-standing by peeling them off the CNT growth support surface, thereby providing free-standing conductive CNT electrode material. In a currently preferred embodiment, the CNT substrate is a well-aligned array of linear CNTs, and the electrically conducting polymer coating free-standing porous substrate electrode is polypyrrole (PPy).

In a further aspect, the present invention provides methods for obtaining CNT electrode materials by coating porous CNT substrates with electrically conductive polymer films. In one embodiment, the coating process comprises coating the CNT substrate with an electrically conductive polymer dissolved in a suitable solvent, followed by removal of the solvent from the coated CNT surfaces by standard method to result in an electrically conductive polymer film

coating. The polymer concentration in the coating solution can be varied to control film thickness. In a preferred embodiment, porous CNT substrates are coated with an electrically conductive polymer film by in-situ polymerization of corresponding monomers from solution directly on the CNT substrate surface. This method provides deposition of substantially uniform, homogeneous and contiguous polymer films that are substantially defect-free, and possess superior electrical properties. Electrically conductive polymers useful for the coating process of the invention include, but are not limited to, polypyrrole (PPy), polyaniline (PAni), polythiophene (PTh), polyacetylene (PA) and their substituted derivatives. The polymer coating preferably is obtained by in-situ solution polymerization of the corresponding monomeric compounds by electrochemical, photochemical or chemical methods. In a currently preferred embodiment, the electrically conducting polymer is PPy, which is obtained by direct electrochemical polymerization from a solution containing the corresponding pyrrole monomer on the surface of the CNT substrate array.

In a currently preferred method, the direct in-situ polymerization of pyrrole on CNT array substrates involves a pre-polymerization de-aeration step wherein nitrogen gas is bubbled through an aqueous electrolyte solution (for example, 0.1M lithium perchlorate ($LiClO_4$))containing dissolved pyrrole monomer for about 30 minutes to eliminate dissolved oxygen. The CNT array substrate materials are pre-treated with an aqueous mineral acid solution, such as for example 15% wt. aqueous HNO_3, for about 30 minutes to remove traces of adherent metallic catalyst particles on individual CNT tubules. The polymerization process is subsequently carried out in a nitrogen atmosphere by standard electrochemical methods. The polymerization reaction is initiated potentiodynamically using a standard three-electrode cell, wherein the CNT substrate functions as one electrode, and a platinum wire functions the counter electrode in the electrolyte solution containing the pyrrole monomer. A saturated calomel electrode (SCE) is used as the reference electrode. The polymerization reaction and the film thickness of the deposited PPy films are monitored by cyclic voltammetry. PPy films are also electro-deposited on the flat metal surfaces (titanium and platinum) in a substantially similar manner to enable comparison of film adhesion and durability in the CNT electrode materials of the invention. All polymerization reactions are carried out at ambient temperature, and all potentials are referred to the saturated calomel electrode (SCE).

Specific attributes and advantages of the electrode materials of the invention, as well as methods for their preparation, are described below with reference to relevant figures.

Figure 1a shows the typical morphology of as grown, aligned CNT array substrate materials comprising a plurality of individually aligned tubules on a nickel coated titanium surface. The individual tubule diameter ranges from about 50 - 100 nm, and tubule length range from about 8 – 10 microns (μm), depending on the layer thickness of the nickel (Ni) catalyst and tubule growth time, respectively. Figure 1b shows well-aligned carbon nanotubes (diameter: 50-70 nanometers (nm), length: 3-4μm) grown on a titanium substrate by plasma-enhanced chemical vapor deposition.

Figure 2 shows the current voltage response during the electrochemical synthesis of PPy films on the well-aligned CNT array substrate material (2a) in comparison with those on flat metal (Pt, and Ti) electrodes (2b, and 2c), respectively. The initial deposition of the PPy film begins at a potential of about 0.4 volts (V) in all cases. The growth behavior on the aligned CNT array substrate material is, however, very different from that on the flat metallic substrates. On flat metallic substrates (e.g. Ti and Pt), the growth current ($\approx$ +0.8V) of PPy is very small (about 3.06×10^{-5} amperes/centimeter^2 (A/cm^2) and 3.91×10^{-4} A/cm^2 for Ti and Pt, respectively) in the first cycle, which then increases in value for each subsequent cycle. This behavior is indicative of a relatively high nucleation energy requirement at the beginning of the PPy film growth on metallic substrates. In contrast, on the aligned CNT array substrates, the current ($\approx$ +0.8V) in the first growth cycle is about 2.57×10^{-3} A/cm^2, which is more than 80 times greater than that on Ti substrate, and about 6.5 times greater than that on the Pt substrate. No significant increase of the current ($\approx$ +0.8V) is observed on the CNT array substrate materials electrode in sequential cycles, while the current ($\approx$ +0.8V) is still much larger than that for either the Ti or Pt substrate. This behavior is attributed to the following: 1) the CNT array substrate material has a substantially high actual surface area due to the nanometer dimensions of individual tubules; 2) the surface of the CNT array substrate is more active (greater surface roughness) than that of flat metallic substrates; a lower nucleation energy is therefore required to initiate surface mediated polymerization of pyrrole; 3) the pre-treatment of CNT array material substrates in aqueous acid solutions, such as aqueous nitric acid, causes tubule surface oxidation, and introduces chemical functional groups on the tubule surface such as carboxylic acids. This enables the resulting oxidized, ionic (anionic) tubules act as a dopant, and improve polymerization of PPy.

Figure 3 shows SEM and TEM micrographs that illustrate the morphologies of PPy-coated conductive CNT electrode material with varying film thickness; comparative the SEM micrographs showing the cross-sectional morphologies of the PPy films grown on flat Ti and Pt substrates are shown in Figure 4. As seen in Figure 3, the coating methods of the present

invention via in-situ polymerization provides highly uniform PPy films on the surface of individual CNT tubules, while the thickness of the PPy film is substantially smaller than those on the flat metal substrates (Figure 4). A film thickness of about 90 nm (Fig. 3d) is typically obtained on the CNT substrate by passing a charge of about 1308.6 millicoulomb/centimeter^2 (mC/cm^2). In comparison, PPy film thicknesses of about 1.1 μm (Fig. 4b) and about 1.5 μm (Fig. 4d), result upon passing a charge of about 645 mC/cm^2 and about 933 mC/cm^2 on Ti on Pt substrates, respectively. The coating methods of the present invention, therefore, provide relatively superior conductive films on CNT array substrate materials in terms of both film uniformity and film thickness (the relatively thinner uniform films are less liable to exhibit defects due to cracking). Such uniform, thin film coatings of electrically conductive polymers on the CNT array substrate of the invention facilitate fast ion diffusion and migration within the polymers, thereby providing superior electrodic performance for the resulting conductive CNT electrode material. Additionally, a high charge capacity and the high charge efficiency for the PPy films can be attained in the conductive CNT electrode material of the invention.

Referring again to Figure 3, a significant morphology difference is observable between PPy films of different thickness and differing film formation charges (Figs. 3a and 3c). When the film formation charge (Q_{film}) is small (Fig. 3a), the PPy coating is thin (about 8 to 10 nm (Fig.3b), and since the PPy-coated CNTs cannot stand individually, this leads to formation of bundles due to surface tension, which comprise an aggregation of a plurality of tubules. With increasing of Q_{film}, the thickness of the PPy film on the tubule surface increases to about 90nm (Fig.3d), thereby strengthening the coated tubules, free-standing tubules are obtained (Fig.3c). As evidenced in these figures, the film uniformity in the coatings obtained by methods of the invention is independent of film thickness, thereby enabling control of film thickness without introduction of coating defects. The free-standing conductive CNT electrode materials of the invention can be rendered detachable as bundles comprising entire arrays from the catalytic surface on which the CNT arrays are grown (Figures 5 (a) – (c)).

Figure 6 shows transmission electron micrographs (TEM) illustrating the morphology of nanotube composites comprising the conductive CNT electrode material of the invention for different PPy film thickness. Figures 6(a) and 6(d) show that the removal of "catalytic caps" (developed during CNT tubule formation and growth) by an acidic pretreatment with aqueous HNO_3 solution, while Figures 6(b) and 6(c) show the presence of the catalyst at the tubule tip. Comparison of Figures 6(a) and 6(d) with 6(b) and 6(c) indicates that the catalyst particle (in this case, Ni) does not affect the electrochemical surface mediated synthesis of PPy films by the

method of the invention. For both types of nanotubes, highly uniform PPy coatings are formed along the length of tubules; PPy film thickness is, however, different. Furthermore, when thickness of PPy film increases, the tubule tips are also covered uniformly by the PPy coating as seen in Figures 6(b), (c) and (d). As seen in Figs. 6(a) and 6(d), no PPy coating deposition occurs on the surface of the inside-wall of the hollow CNT tubules although the tip is open. This is indicative of the fact that the electrolyte solution, due to surface tension effects, does not enter the tubules during PPy deposition. From the TEM micrographs shown in Figures 6(a) - (d), the thickness of PPy film and the diameter of the nanotube are related. The relationship tubule parameters, including diameter and length, Q_{film}, PPy film thickness, and the ratio of Q_{film} to of PPy film thickness is shown in Table 1. These results show that thickness of the PPy film is linearly proportional to Q_{film} up to about 681.9 mC/cm^2, suggesting that PPy film thickness can be controlled easily by Q_{film} before reaching critical Q_{film} (onset of non-linearity) by the method of the invention. Figure 6(e) further shows that the PPy coating along a long length of individual tubules is contiguous and uniform, indicating that they do not touch each other during the electro-deposition polymerization method of the invention. The separation of individual tubules from each other may be due to surface charges that repel them from each other, resulting in non-contact between adjacent tubules during the polymerization process.

Contrary to conventional thick film ECPs on the flat substrates that peel off the substrate easily (for example, a PPy film peels off easily from Pt surfaces even when the film is relatively thin (Q_{film} is about 933 mC/cm^2), the ECP films on the CNT substrates of the present invention exhibit good adhesion between the CNT substrate the ECP film. PPy films obtained by the methods of the invention do not peel off from the CNT substrate at relatively higher film thickness (when Q_{film} is great as 1308.6 mC/cm^2). Most known conventional ECPs, such as PPy, PAni, etc., are mechanically weak. Strengthening of ECP films is typically achieved by the following: 1) co-polymerization of the ECP monomer with a second polymer such as poly(vinylchloride) (PVC) to produce mechanically superior films, which however, results in sacrifice of film electrical conductivity; 2) formation of composites with carbon materials, such as carbon black, that are limited by film non-uniformity, inadequate control of film thickness and coating defects. The in-situ polymerization coating methods on the CNT array substrates of the present invention overcome such limitations, imparting both high strength and excellent electrical conductivity to fabricated conductive CNT electrode materials, and rendering them capable of exhibiting superior electrodic performance in electrical storage devices.

Table 1. Relation between the nanotube parameters, film formation charge (Q_{film}), PPy film thickness, and Q_{film} /PPy thickness ratio.

Sample	Diameter/Length of nanotubes (nm/μm)	Q_{film} (mC/cm^2)	Thickness of PPy films (nm)	Q_{film}/ PPy Film Thickness
1	90~110/10	86.1	10	8.61
2	80~100/13	207.9	22	9.45
3	100~120/5	681.9	76	8.97
4	30~50/7	1308.6	93	14.07

Figure 7 shows the cyclic voltammetry curves illustrating the influence of the CNT substrate on redox behavior of the surface coated thin PPy films in the conductive CNT electrode materials of the invention, and on reference flat metal surfaces (Pt and Ti). The redox curves shown in Figure 7 are superimposed on a "capacitive" background, in a standard manner that is typically used in cyclic voltammetry measurements of conducting polymers, including PPy. For the uncoated CNT substrate, no significant redox peaks are observable from –0.9V to +0.3V in $LiClO_4$ aqueous solution. For the CNT electrode of the invention comprising a PPy-coated conductive CNT electrode material of the invention, on the other hand, the following differences are observed: 1) the charge increases at the negative end of the potential window, and redox behavior is observed at about -0.55V; 2) a higher current density is observed at about -0.9V, at which PPy is essentially electrically insulating. This is indicative of an enhanced electronic conductivity of the PPy film on the CNT array substrate for the conductive CNT electrode material of the invention, especially at negative potential, which is an important characteristic for a conductive polymer material to be applied in a reducing environment; 3) an enhancement in specific charge capacity relative to PPy on flat Pt/Ti surface is also observed for the conductive CNT electrode materials of the invention.

Figure 8 shows cyclic voltammograms of the conductive CNT electrode materials of the invention containing PPy films of varying thickness in comparison to similar films grown on planar metallic substrates by the coating method of the invention. The cyclic voltammograms of

PPy films on Pt, Ti, and a CNT array substrate with different thickness are shown in Figures 8a, 8b, and 8c, respectively. Although a similar trend is evident for PPy films on Pt and Ti, and the CNT array substrate, the charge-discharge rates for Pt and Ti surfaces are strongly influenced by the polymer film thickness (when Q_{film} increases, i.e., the PPy film becomes thick, peak separation potential (ΔE_p) increases and the typical charge-voltage (CV) characteristic of PPy gradually decreases). The CV characteristic of PPy-coated CNT electrode materials, on the other hand, unlike for Pt and Ti surfaces, is not significantly influenced by film formation charge (Q_{film}).

Figure 9 shows the a comparison of the doping-undoping kinetics of PPy films deposited with large Q_{film} for a normalized redox current by Q_{film} in the conductive CNT electrode material of the invention. As evidenced in the figure, the CNT array substrate comprising the base for the conductive CNT electrode material speeds up the redox process. While the well-defined CV redox peaks disappear when Q_{film} is about 645 mC/cm^2 for a PPy coated flat Ti substrate, a well-defined CV can is observable even when Q_{film} is as high as 1308 mC/cm^2 for the PPy-coated conductive CNT electrode material of the invention. Further, the specific charge capacity of the PPy-coated conductive CNT electrode material is also greater than that of PPy films coated on flat metallic surfaces.

Figure 10 shows the influence of electrically conductive polymer film formation charge (Q_{film}) on the redox charge (Q_{redox}) for the conductive CNT electrode material of the invention (which is estimated from the anodic charge illustrated in the cyclic voltammograms), in comparison to corresponding film formation on flat metallic substrates. In general, Q_{redox} increases with Q_{film} prior to reaching a certain threshold value, whereupon it starts to decrease with further increase of Q_{film}. It is evident from Figure 10 that the difference is that Q_{redox} increases with Q_{film} more rapidly for the conductive CNT electrode materials of the invention containing a PPy-coating than similarly coated conventional flat electrodes comprised of metallic Pt and Ti substrates. Specifically, when Q_{film} is around 680 mC/cm^2, Q_{redox} improvements of about 2.5 and about 23 times have been achieved for the PPy coated conductive CNT electrode materials of the invention in comparison to PPy coated on flat Pt and Ti substrates, respectively.

The present invention provides conductive CNT electrode materials for the construction of electrodes possessing substantially improved electrochemical redox performance for use in electrical energy storage devices. Such characteristics are important for construction of lightweight high-efficiency devices such as rechargeable batteries. The conductive CNT

electrode materials of the invention enable the utilization of thin, highly uniform films of electrically conducting polymers as stable, adherent surface coatings on carbon substrates of high surface area, particularly CNT substrates with well-aligned tubule morphologies. The electrical conductivity of the conductive CNT electrode materials of the invention can be further enhanced by introduction of suitable dopant materials in the conductive polymer coating. The dopant materials may be either n-type such as molecular iodine (I_2), or p-type such as tetrathiafulvalene (TTF) and tetracyanoquinodimethane (TCNQ) that can be introduced by standard methods. The in-situ polymerization of monomers directly on the substrate surface utilizing the CNT array substrates and methods of the invention enables the deposition of uniformly thin films of electrically conducting polymers such as PPy as defect free coatings with superior electrical properties, enable their use as electrodes in the manufacture of high-efficiency, light weight electrical storage devices, in comparison to conventional devices utilizing electrodes comprising coated flat metal substrates. The electrochemical in-situ polymerization method of the invention provides polymer growth currents, particularly for PPy, on the aligned CNT array substrates that is substantially greater than that on the flat Ti and Pt substrates, and the resulting conductive CNT electrode materials show significant improved electrochemical redox performance, especially for PPy films with large Q_{film}. The significantly enhanced redox charge of PPy films in the PPy coated CNT array substrates of the invention in comparison to conventional flat Ti and Pt substrates, enables their use as hybrid materials in high-performance light-weight rechargeable batteries.

Although examples are used herein to describe the invention in detail, it is understood that such detail is solely for the purpose of example, and variations and modifications can be made therein by those skilled in the art without departing from the spirit and scope of the invention.

EXAMPLES

Example 1

Synthesis of well-aligned carbon nanotubes (CNTs)

Well-aligned carbon nanotubes were obtained by methods disclosed in the art (see Z.F. Ren, et al., Science 282 (1998) 1105; Z.P. Huang et al. Appl. Phys. Lett. 73 (1998) 26; Z.F. Ren, et al., Proceedings of the 13th International Winter School on Electronic Properties of Novel Materials, (1999) 263; Z.F. Ren, et al., Appl. Phys. Lett., 75 (1999) 1086; and Z.F. Ren, et al.,

Proceedings of the 32nd International Technical Conference of the Society for the Advancement of Materials and Process Engineering (SAMPE), Nov. 5-9, 2000, Boston, USA, pp. 200-204). Titanium (Ti) is used as base substrate upon which a thin nickel (Ni) layer of about 15 – 25 nm was surface coated by magnetron sputtering to function as a catalyst for CNT growth. The CNTs obtained by this method have tubule diameters ranging from 50 - 100 nm and tubule lengths of 8 - 10 μm. Tubule diameter and length is controlled by varying the Ni layer thickness and growth time, respectively.

Example 2

PPy deposition and electrochemical measurements

PPy films were deposited on CNT substrates by in-situ polymerization of pyrrole potentiodynamically using a standard three-electrode cell from 17.3mM pyrrole (Aldrich) and 0.1M $LiClO_4$ (Aldrich, A.C.S reagent) aqueous solutions. A *PC4* potentiostat / Galvanostat (Gamary Instruments Inc., Warminster, PA 18974) was employed for the synthesis and cyclic voltammetric (CV) measurements of PPy films. Platinum wire was used as the counter electrode, and a saturated calomel electrode (SCE) was used as the reference electrode. Prior to PPy deposition, the CNT substrates were pretreated in 15% wt. HNO_3 aqueous solution for 30 minutes to remove non-adherent metallic Ni catalyst particles and also to increase electrochemical activity of the surface of the CNTs in water and aqueous solutions. After PPy deposition, the substrates were soaked in double distilled water for 30 minutes to remove unreacted pyrrole monomer. Redox processes of the PPy-coated carbon nanotube electrodes were measured in monomer-free 0.1M $LiClO_4$ aqueous solution. Both prior to PPy deposition and the redox study, the solution was bubbled with nitrogen for 30 minutes to eliminate oxygen, and during the experiments, nitrogen gas was used as the protecting atmosphere. For comparison, PPy films were also electro-deposited on the flat metal substrates (titanium and platinum). In order to improve the adhesion of PPy on flat titanium (Ti) substrate, the pretreatment of Ti in dilute nitric acid (15% wt.) was carried out before the PPy deposition. All experiments were made in ambient temperature. All the potentials were referred to the saturated calomel electrode (SCE).

Example 3

Characteristics of PPy Films polymerized on CNT substrates

Film Thickness

PPy coatings obtained on CNT substrates via the in-situ polymerization methods provides highly uniform films on the surface of individual CNT tubules. A typical film thickness of about 90 nm is obtained by passing a charge of about 1308.6 mC/cm^2 on the outer surface of individual tubules. In comparison, film thickness of about 1.1 μm and about 1.5 μm, are obtained upon passing a charge of about 645 mC/cm^2 and about 933 mC/cm^2 on Ti and Pt surfaces respectively.

Film Morphology

PPy film morphologies are dependant on film thickness film formation charge (Q_{film}). A small film formation charge (Q_{film}) results in a thin PPy coating (about 8 to 10 nm), coated CNT substrates that are not free-standing. The CNT tubules form bundles as a result of surface tension. With increase in Q_{film}, the thickness of the PPy films on the tubule surface increases to about 90nm, providing mechanically strong, coated tubules that are free-standing. Such coated CNT substrates (CNT electrode materials), comprising CNT tubule arrays, are entirely detachable from CNT catalyst surfaces.

Example 4

Electrical properties of CNT electrode materials

Redox peaks for uncoated CNT substrates are insignificant in the range of about –0.9V to about +0.3V in $LiClO_4$ aqueous solution. For the CNT electrode materials (PPy coated CNT substrate) the electrical charge increases at the negative end of the potential window, and redox behavior is observed at about -0.55V. A higher current density is also observed at about -0.9V, at which PPy is essentially electrically insulating. The charge-discharge rates are strongly influenced by the PPy film thickness. The peak separation potential (ΔE_p) increases with increasing film formation charge (Q_{film}) increases, i.e., the PPy film becomes thick, and the typical CV characteristic of PPy gradually decreases). The current-voltage (CV) characteristic for the CNT electrode materials remains substantially independent of by film formation charge (Q_{film}).

CLAIMS

What is claimed is:

1. A conductive carbon nanotube electrode material comprising:

a carbon nanotube substrate comprising a plurality of aligned carbon nanotubes arranged in a three-dimensional array; and

a surface coating comprising an electrically conductive material that is present as a film on the surface of the individual carbon nanotubes in the array,

wherein a majority of said carbon nanotubes are randomly aligned within a series of mutually parallel planes in a manner so as to be packed densely enough to produce multiple points of contact thereamong, whereby electrical continuity is established throughout said three-dimensional array.

2. The conductive carbon nanotube electrode material of claim 1 wherein the carbon nanotubes have a substantially linear configuration.

3. The conductive carbon nanotube electrode material of claim 1 wherein the carbon nanotubes have a substantially cylindrical, hollow core morphology.

4. The conductive carbon nanotube electrode material of claim 1 wherein the carbon nanotubes have a stacked conical segment morphology.

5. The conductive carbon nanotube electrode material of claim 1 wherein the carbon nanotubes have diameters ranging from 30 and 100 nanometers.

6. The conductive carbon nanotube electrode material of claim 1 wherein the carbon nanotubes have lengths ranging from 5 to 10,000 nanometers.

7. The conductive carbon nanotube electrode material of claim 1 wherein the electrically conductive material is an electrically conducting polymer.

8. The electrically conducting polymer of claim 7 which is an organic or organo-metallic polymer.

9. The electrically conducting polymer of claim 7 which is polypyrrole, polyaniline, polythiophene, polyacetylene or derivatives and combinations thereof.

10. The electrically conducting polymer of claim 7 wherein the electrically conducting polymer is polypyrrole.

11. The conductive carbon nanotube electrode material of claim 1 wherein the electrically conducting material further comprises a dopant.

12. The conductive carbon nanotube electrode material of claim 1 wherein the surface coating has a film thickness ranging from 1 to 2,000 nanometers.

13. The carbon nanotube electrode material of claim 10 wherein the coating has a thickness ranging from 50 nanometers to 200 nanometers.

14. The conductive carbon nanotube electrode material of claim 1 wherein a plurality of carbon nanotubes form a free standing aggregate.

15. The conductive carbon nanotube electrode material of claim 14 wherein the free standing aggregate comprises a plurality of carbon nanotubes that are substantially aligned with one another along their longitudinal axis.

16. A carbon nanotube electrode comprising a conductive carbon nanotube electrode material of claim 1 wherein a majority of said nanotubes are randomly aligned within a series of mutually parallel planes in a manner so as to be packed densely enough to produce multiple points of contact thereamong, whereby electrical continuity is established throughout said three-dimensional array.

17. The carbon nanotube electrode of claim 16 further comprising a plurality of carbon nanotubes that packed together in the form of an aggregate that is cohesively bound together by the electrically conductive coating material so as to enable said aggregate to exist in a free-standing form.

18. The carbon nanotube electrode material of claim 17 wherein the electrically conductive coating material is polypyrrole.

19. An electrical energy storage device comprising:

an electrically conducting carbon nanotube electrode comprising a plurality of carbon nanotubes in a three-dimensional array; and

an electrically conducting material that is present as a uniform surface coating on the surface of individual nanotubes,

wherein a majority of said nanotubes are randomly aligned within a series of mutually parallel planes in a manner so as to be packed densely enough to produce multiple points of contact thereamong, whereby electrical continuity is established throughout said three-dimensional array.

20. The electrical storage device of claim 19 wherein the electrical storage device is a battery, an energy storage cell, a sensor, a light-emitting diode, a capacitor, or an electrochromic display.

21. The electrical storage device of claim 20 which is a rechargable battery.

22. A method of preparing an electrically conductive aligned carbon nanotube array comprising the steps of:

contacting a carbon nanotube substrate comprising a plurality of substantially linear mutually aligned carbon nanotubes with a monomeric compound capable of forming an electrically conducting polymeric material that is dissolved in an aqueous or organic solvent containing an electrolyte material such that said carbon nanotube substrate functions as a first electrode in an electrochemical cell;

introducing a second electrode material to form a second electrode in the electrochemical cell; and

applying an electrical potential between the first electrode and the second electrode to cause an electrochemical polymerization of the monomeric compound to the corresponding electrically conducting polymer whereby said electrically conducting polymer provides an adherent surface coating on the individual carbon nanotubes.

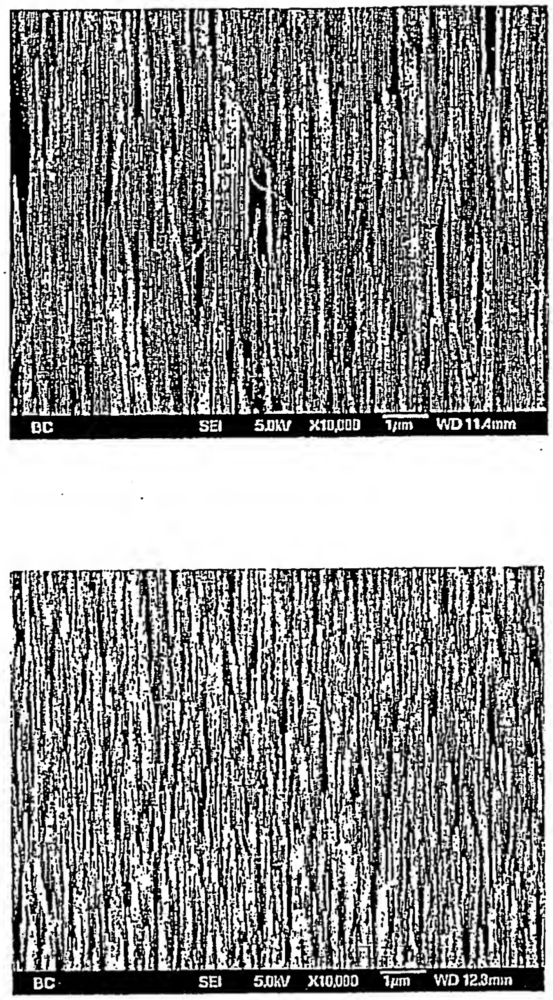
23. The method of claim 22 wherein the electrochemical polymerization of the monomeric compound occurs directly on the surface of individual carbon nanotube.

24. The method of claim 22 further comprising the step of pre-treating the carbon nanotube substrate material with an acid solution.

25. The method of claim 24 wherein the acid solution is an aqueous solution of nitric acid, sulfuric acid, chromic acid, an organic per acid or mixtures thereof.

26. The method of claim 24 wherein the acid solution is an aqueous solution of nitric acid.

27. The method of claim 26 wherein the acid solution contains nitric acid ranging from 5 to 50% by weight.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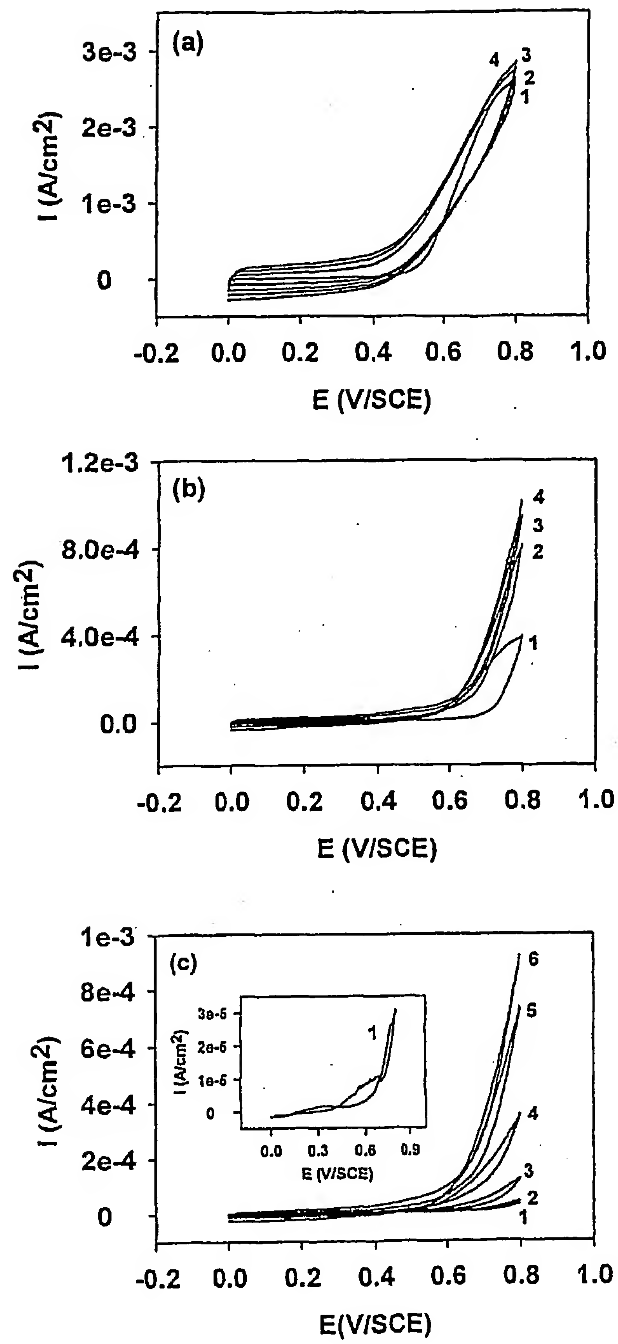
BC SEI 5.0kV X10,000 1μm WD 12.3mm
(a)

(b)

Figure 1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1e-3
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0.0
0.2
0.4
0.6
0.8
1.0
E (V/SCE)
1
2
3
4
(b)
I (A/cm2)
1.2e-3
8.0e-4
4.0e-4
0.0
E (V/SCE)
(c)
I (A/cm2)
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6e-4
4e-4
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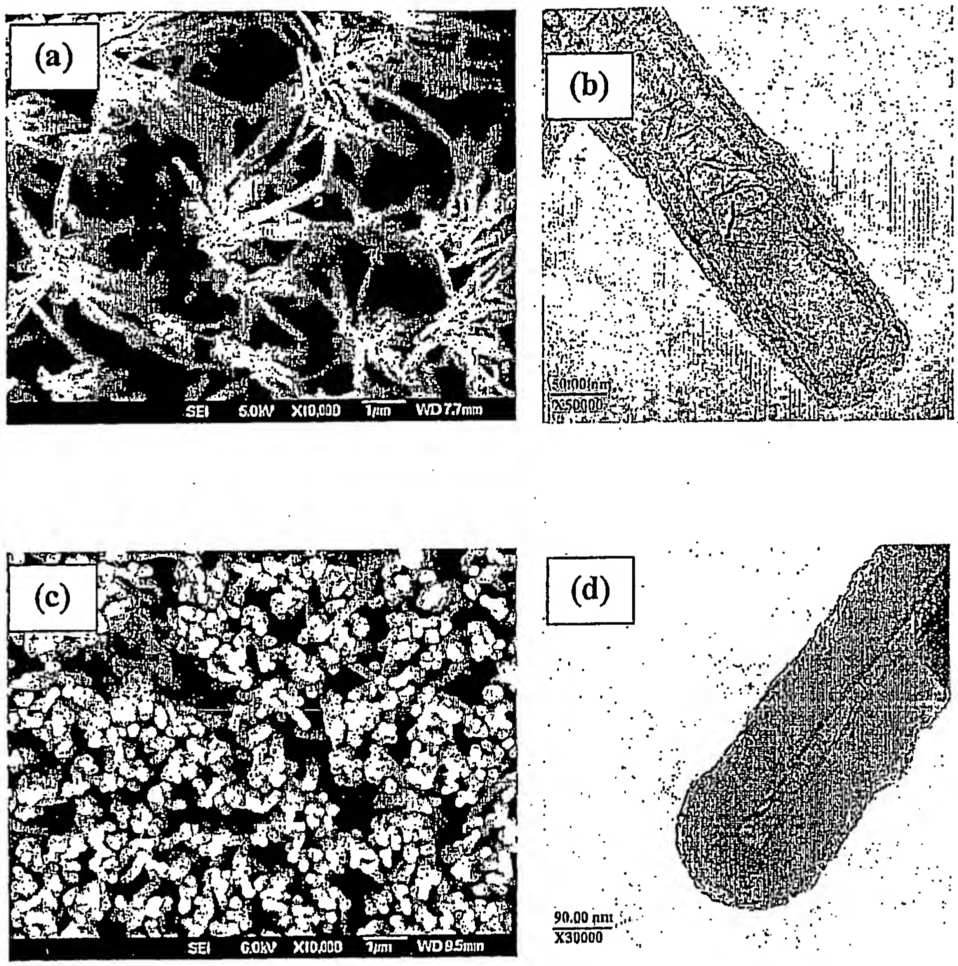
2e-5
1e-5
0.3
0.9
E (V/SCE)

Figure 2


(a)
SEI 5.0kV X10,000 1μm WD 7.7mm
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(c)
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(d)
90.00 nm
X30000

Figure 3

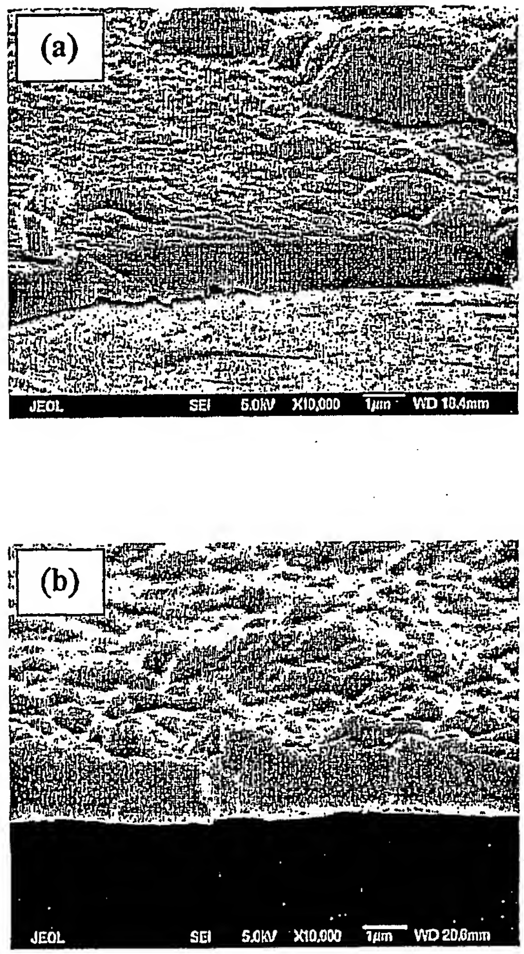
(a)
JEOL SEI 5.0kV X10,000 1μm WD 10.4mm
(b)
JEOL SEI 5.0kV X10,000 1μm WD 20.0mm

Figure 4

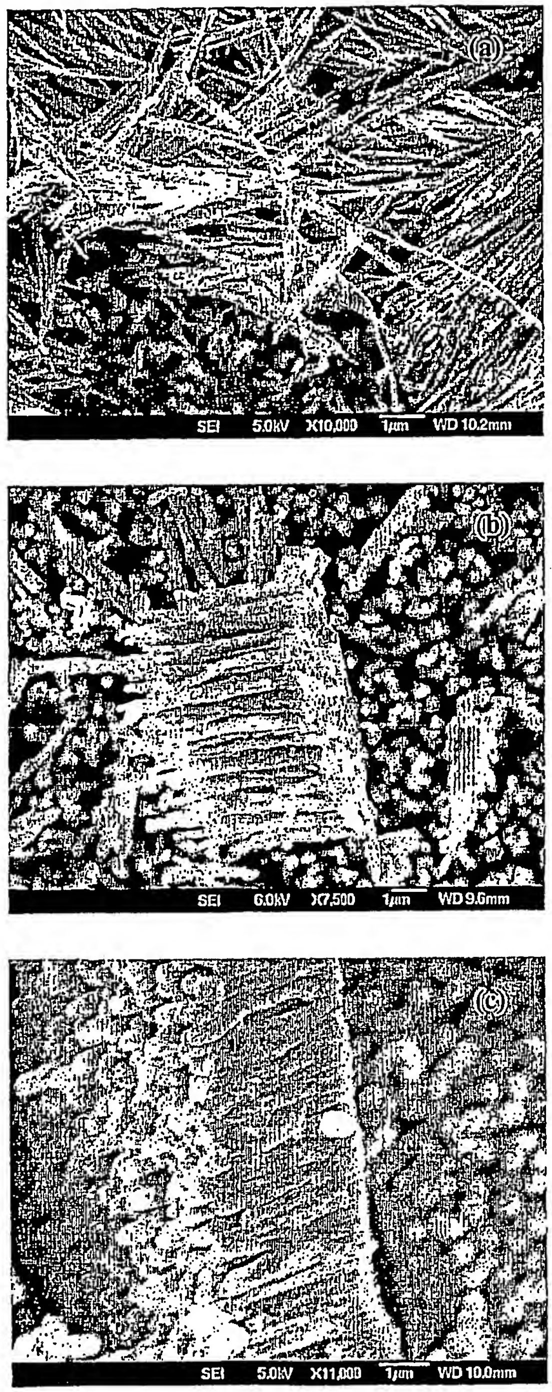
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Figure 5

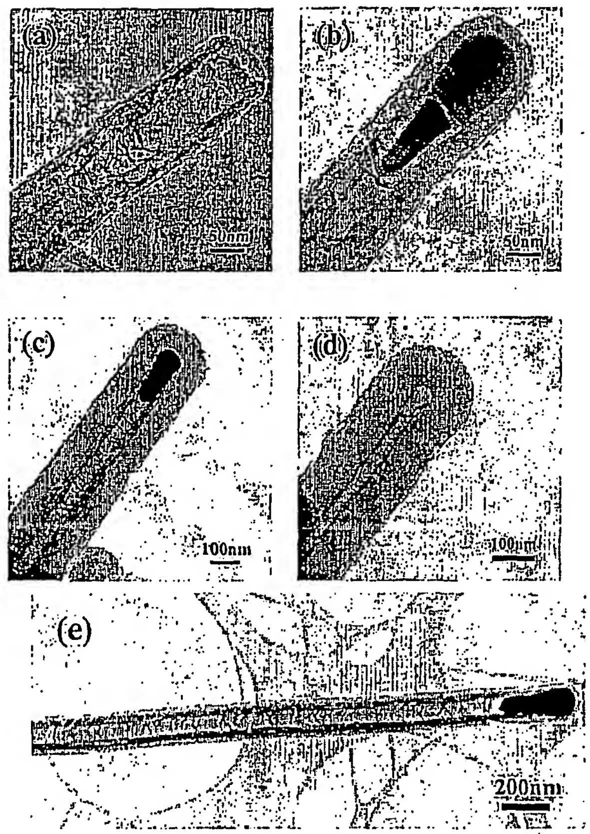


Figure 6

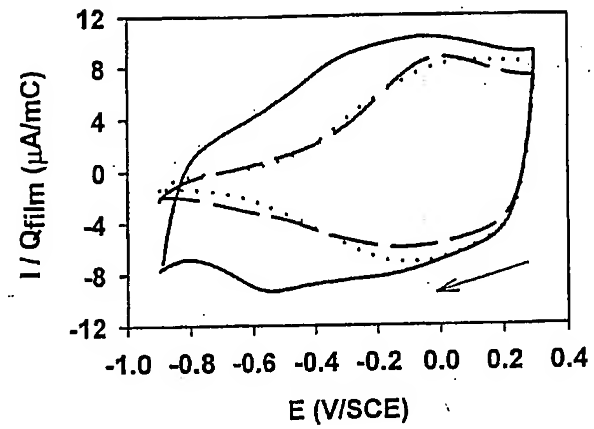
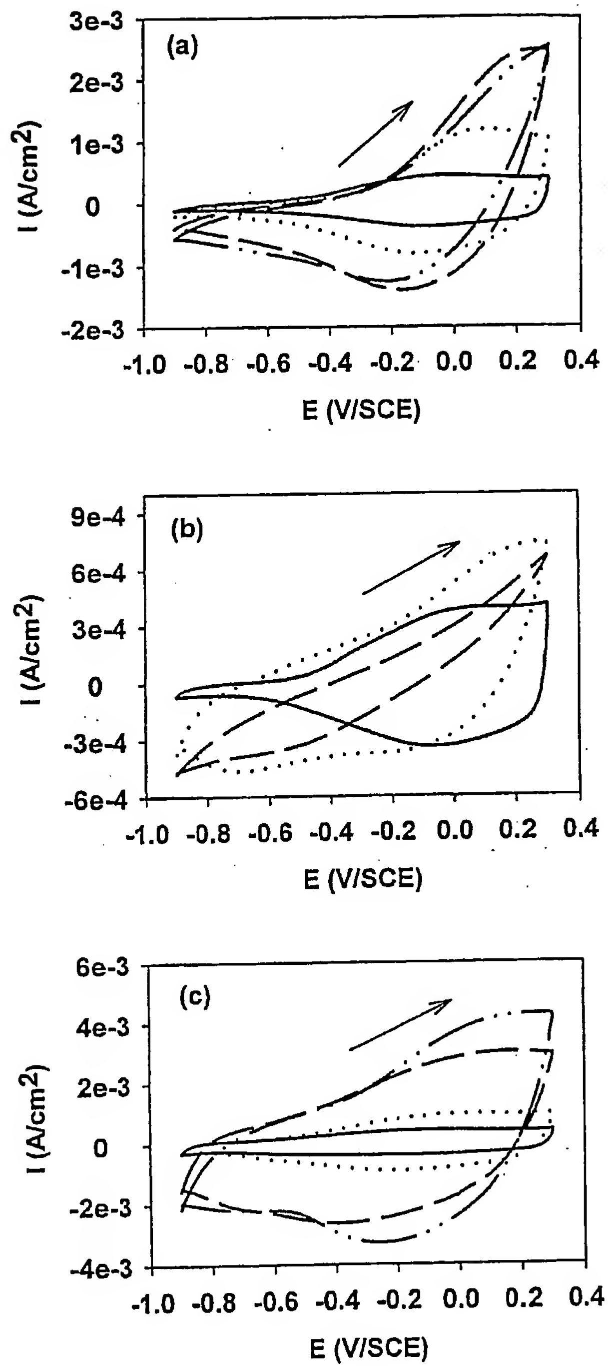


Figure 7


(a)
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1e-3
0
-1e-3
-2e-3
I (A/cm2)
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E (V/SCE)
(b)
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6e-4
3e-4
0
-3e-4
-6e-4
I (A/cm2)
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E (V/SCE)
(c)
6e-3
4e-3
2e-3
0
-2e-3
-4e-3
I (A/cm2)
-1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2 0.4
E (V/SCE)

Figure 8

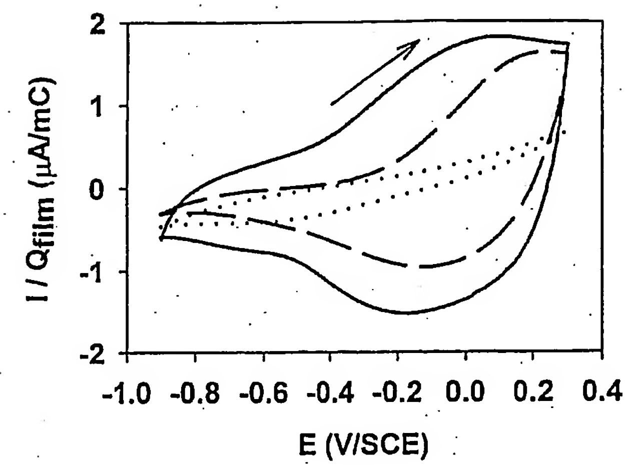

Figure 9

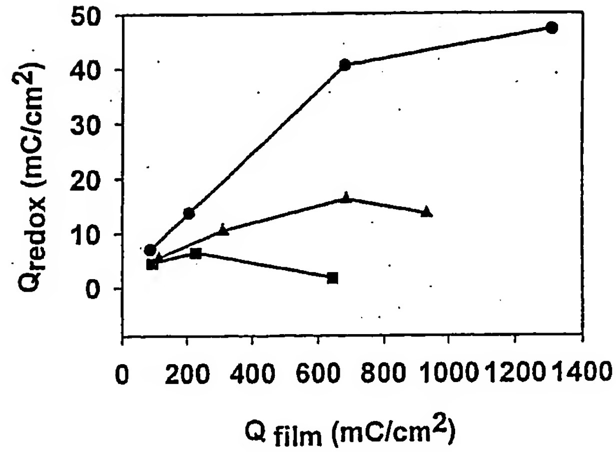
50
40
30
20
10
0
Qredox (mC/cm2)
0 200 400 600 800 1000 1200 1400
Q film (mC/cm2)

Figure 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/38262

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : H01M 4/96, 4/60
US CL : 429/218.1, 231.4, 231.8; 423/445R, 445B
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 429/218.1, 231.4, 231.8; 423/445R, 445B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2000-277002A (NAKAYAMA et al.) 06 October 2000 (06.10.2000), paragraphs 39-41 and Fig. 2.	1-3, 7, 8, 19, 20, 22
X	US 2001/0023986 A1 (MANCEVSKI) 27 September 2001 (27.09.2001), paragraphs 40 and 89 and Fig. 2.	1-3, 6, 14, 15, 19
X, P	US 2002/0153160 A1 (HOFMANN et al.) 24 October 2002 (21.10.2002), paragrphs 14-20 and Fig. 1.	1-3, 16, 19
X, P	US 2001/0051367 A1 (KIANG) 13 December 2001 (13.12.2001), paragrphs 21-22 and 28-29, Figs. 1-3.	1-3, 6-9
A	US 6,099,960 A (TENNENT et al.) 08 August 2000 (08.08.2000), the entire document.	1-27
A	US 6,205,016 B1 (NIU) 20 March 2001 (20.03.2001), the entire document.	1-27
A	US 6,283,812 B1 (JIN et al.) 04 September 2001 (04.09.2001), the entire document.	1-27
A	US 6,312,303 B1 (YANIV et al.) 06 Noember 2001 (06.11.2001), the entire document.	1-27

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 09 March 2003 (09.03.2003)	Date of mailing of the international search report 20 MAR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Carol Chaney Jean Proctor Paralegal Specialist Telephone No. 703-308-0661

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/38262

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(21) International Application Number: PCT/US03/13289

(22) International Filing Date: 1 May 2003 (01.05.2003)

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(71) Applicant (*for all designated States except US*): **DUKE UNIVERSITY** [US/US]; Erwin Road, Durham, NC 27706 (US).

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(74) Agents: **BROOK, David E.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/092763 A1

(54) Title: CARBON NANOTUBULES FOR STORAGE OF NITRIC OXIDE

(57) Abstract: Delivering nitric oxide to a treatment site, such as in the area of an implanted stent, over a period of hours or days is desirable; however, the storage and release of nitric oxide in medically-relevant situations and amounts is a challenge, in part due to the gaseous nature of nitric oxide and its instability in the presence of oxygen, The present invention provides a method of preparing compositions of matter, particularly those comprising nanotubules, containing nitric oxide or gases with nitric oxide-like biological activity, where the gas is non-covalently bound to the composition. These compositions allow for the storage of nitric oxide or a related gas, followed by controlled release of the gas. Compositions disclosed in the present invention include polymers, articles, pills, capsules, and medical devices.

CARBON NANOTUBULES FOR STORAGE OF NITRIC OXIDE

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/377,862, filed May 3, 2002. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Nitric oxide is a small, gaseous molecule produced endogenously by both plants and animals. In animals, nitric oxide has particularly important effects in the circulatory, immune, and nervous systems. The effects on the circulatory system include regulation of blood pressure through relaxation of the smooth muscle walls of blood vessels and prevention of clotting by inhibiting the aggregation of platelets. The release of nitric oxide in close proximity to a medical device such as a stent or an artificial heart is expected to reduce the clotting encountered with these devices, thereby reducing morbidity and mortality.

Several difficulties have been encountered in storing nitric oxide in a discrete source and delivering nitric oxide to a treatment site over a period of days or weeks. For example, nitric oxide has a short half-life, on the order of seconds, in oxygenated milieu, particularly biological milieu. Also, as a gas, nitric oxide tends to rapidly diffuse away from point sources, preventing it from being efficiently stored.

In the place of nitric oxide, various compounds, which are relatively stable in the presence of oxygen, have been used. These compounds release nitric oxide or molecules with nitric oxide-like activity upon exposure to acids, bases, metal ions, light, heat, and the like. Nitric oxide-releasing compounds include S-nitrosothiols, diazeniumdiolates (NONOates), organic nitrites, organic nitrates (e.g., nitroglycerin), metal nitrosyls (e.g., sodium nitroprusside), and nitrosylated proteins and peptides. These all represent effective sources of nitric oxide, however, the nitric oxide activity relies on a reaction to convert the above sources into nitric oxide. It is desirable to have an authentic source of nitric oxide that does not necessarily rely on the presence of enzymes, metal ions, or free thiols to convert a precursor molecule into nitric oxide.

It is therefore desirable to develop a device or composition for storing nitric oxide or a gas with nitric oxide-like activity, which allows for storage and prolonged release of the gas and does not involve covalently bonding nitric oxide or a related gas to the device.

SUMMARY OF THE INVENTION

It has now been found that nitric oxide can be contained in hydrophobic materials, particularly nanotubules, such that nitric oxide can be stored by a hydrophobic material. It has also been found that nitric oxide can be slowly released by such hydrophobic materials over extended periods of time. For example, carbon nanotubules loaded with nitric oxide released nitric oxide continuously for over a day (Example 3), even when the nanotubule was entrained in a styrene-isobutylene copolymer (Example 5). In addition, the nitric oxide released from these nanotubules retains its biological activity. For example, rabbit aortal rings relaxed when exposed to nitric oxide-loaded carbon nanotubules (Example 2). Based on these discoveries, novel nitric oxide-containing nanotubules and methods of preparing and using such nanotubules are disclosed herein.

In one embodiment, the present invention is a composition comprising a compound that non-covalently binds nitric oxide or a gas with nitric oxide-like

biological activity. Nitric oxide or a gas with nitric oxide-like biological activity is non-covalently bound to said compound. Suitable compositions include surfactants, perfluorocarbons, polythiolated cyclodextrins, and cyclodextrins.

The present invention includes a nanotubule, where the nanotubule contains nitric oxide or a gas with nitric oxide-like biological activity. The interior of the nanotubule is substantially free of oxygen.

The present invention also includes an article comprising one or more nanotubules, which each contain nitric oxide or a gas with nitric oxide-like biological activity.

In another embodiment, the present invention is a method of administering nitric oxide or a gas with nitric oxide-like properties to an individual, comprising the step of contacting an aqueous solution with an article of the present invention and administering the aqueous solution to the individual. Articles, which can be advantageously used in this method, include bags containing intravenous fluid, syringes, and medical tubing.

The present invention is also a polymer entrained with nanotubules, where the nanotubules contain nitric oxide or a gas with nitric oxide-like biological properties.

The present invention includes a method of delivering nitric oxide to a treatment site by implanting a medical device comprising one or more nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity.

In another embodiment, the present invention is a method of preparing nanotubules comprising nitric oxide or a gas with nitric oxide-like biological activity. The method comprises the step of contacting the nanotubules with nitric oxide or a gas with nitric oxide-like biological activity, where the nitric oxide or the gas with nitric oxide-like biological activity is substantially free of oxygen.

The present invention has many advantages. Compositions of the present invention have the ability to store therapeutically relevant quantities of nitric oxide or related gases in an uncomplexed form. These compositions also have the ability to release stored nitric oxide in a controlled fashion, thereby serving as a long-acting source of nitric oxide. These compositions are easily prepared, by contacting a

material with nitric oxide or a gas with nitric oxide-like biological activity under pressures at or exceeding ambient pressure.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the release of nitrogen oxides (N_{ox}) from nanotubules loaded with nitric oxide into phosphate-buffered saline (PBS) at 37°C.

Figure 2 is a graph showing the release of nitrogen oxides (N_{ox}) from nanotubules loaded with nitric oxide entrained in a styrene-isobutylene-styrene copolymer (SIBS) into phosphate-buffered saline at 37°C.

DETAILED DESCRIPTION OF THE INVENTION

Compositions of the present invention comprise compounds which bind nitric oxide or a gas with nitric-oxide like properties non-covalently. Although Applicants do not wish to be bound by any particular mechanism, it is believed that the binding results from pi stacking, van der Waals forces, and/or hydrophobic interactions. Typically, such compositions and compounds are hydrophobic. One example of a composition of the present invention is a nanotubule containing nitric oxide or a gas with nitric oxide-like biological activity. Other compositions capable of non-covalently binding nitric oxide or a gas with nitric oxide-like properties include surfactants, perfluorocarbons, polythiolated cyclodextrins, and cyclodextrins. Another example is a composition comprising a polymer and nanotubules entrained in the polymer, where the nanotubules contain nitric oxide or a gas with nitric oxide-like biological activity.

Nanotubules of the present invention can be characterized as long symmetrical carbon tubes, which are formed from hexagonal and pentagonal graphite molecules joined at their edges. Nanotubules can additionally comprise heteroatoms or metals. Nanotubules typically have diameters of about 1 nm to about 50 nm, about 2 nm to about 25 nm, or about 5 nm to about 10 nm. Nanotubules typically have lengths of about 10 nm to about 100 μm, about 100 nm to about 10 μm, or about 500 nm to about 2 μm. Nanotubules of the present invention can be single-walled or multi-walled, where one or more single-walled nanotubules are

contained within a nanotubules of greater diameter and equal or greater length. Nanotubules can have "zigzag", armchair, helical, spiral, twisted, and untwisted shapes and geometries. Nanotubules of these types are known in the art and are disclosed, for example, in M.S. Dresselhaus, G. Dresselhaus, P.C. Eklund, "Fullerenes," *J. Mater. Res.*, 8(8), 2054-2097, (1993); P.E. Ross, "Buckytubes," *Sci. Am.*, 24, (Dec. 1991); B.I. Yakobson and R. Smalley, "Fullerene Nanotubes: C1,000,000 and Beyond," *Am. Sci.*, 85(4), 324-337 (1997); J. Bernholc, C. Roland, and B.I. Yakobson, "Nanotubes," *Curr. Opin. Solid State Mater. Sci.*, 2, 706-715 (1997), the entire teachings of which are incorporated herein by reference.

Nanotubules of the present invention contain nitric oxide or a gas with nitric oxide-like biological activity. Preferably, nanotubules of the present invention contain nitric oxide. Typically, nitric oxide or the gas with nitric oxide-like activity contained by the nanotubule comprises about 0.5 weight percent to about 10 weight percent, about 0.5 to about 6 weight percent, about 0.5 to about 4 weight percent, or about 1 to about 3 weight percent of the nanotubule. Gases with nitric oxide-like biological activity include nitrogen dioxide, dinitrogen trioxide, and alkyl nitrites. Alkyl nitrites include ethyl nitrite, propyl nitrite, *n*-butyl nitrite, *iso*-butyl nitrite, amyl nitrite, and *iso*-amyl nitrite.

As defined herein, nitric oxide or a gas with nitric oxide-like biological activity is "contained" in a nanotubule when it is in the interior of such nanotubules or adsorbed on the interior or exterior surface of such nanotubules.

The interiors of nanotubules of the present invention are typically substantially free of oxygen. "Substantially free of oxygen," as defined herein, means the interior of a nanotubule contains less than 5% oxygen by volume, preferably containing less than 2% oxygen by volume, even more preferably contains less than 1% oxygen by volume, and most preferably contains no oxygen.

Nanotubules of the present invention can optionally be functionalized with one or more functional groups on either the sides or the ends of a nanotubule. Optionally, 0 to 50% of the carbon atoms of a nanotubule can be functionalized. A wide variety of reactive groups can serve as functional groups, including those comprising nitrogen, oxygen, sulfur, phosphorus, and halides, particularly fluoride.

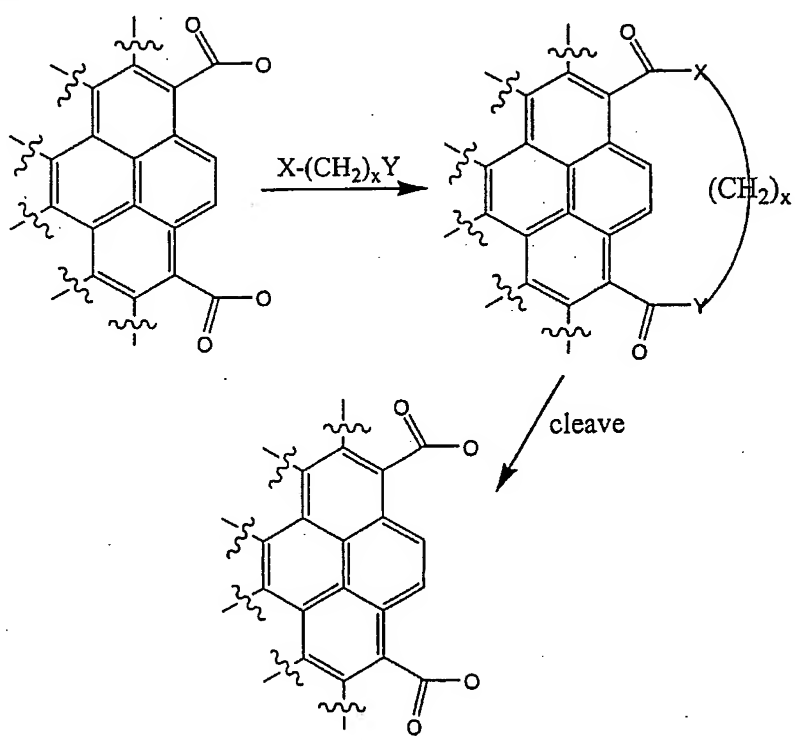
In one example, the sides of a nanotubule are fluorinated by reacting a nanotubule with elemental fluorine. In another example, the ends of a nanotubule are functionalized with carboxylic acid or carboxylate groups. Functional groups (or functionalized nanotubules) can undergo further reaction, for example, a fluorinated nanotubule (e.g., one containing C-F bonds) can be reacted with an alkoxide, an alkyllithium complex, or a Grignard reagent (an alkylmagnesium bromide) to form an alkoxylated or an alkylated nanotubule. Typically, a functional group will not decrease the nitric oxide content (e.g. measured by weight percent nitric oxide) of a nanotubule more than two-fold, and preferably increases the nitric oxide content of a nanotubule. Functionalized nanotubules of these types are known in the art and are disclosed, for example, in E.T. Mickelson, I.W. Chiang, J.L. Zimmerman, P.J. Boul, J. Lozano, J. Liu, R.E. Smalley, R.H. Hauge, J.L. Margrave, *J. Phys. Chem.*, 103, 4318-4322 (1999) and P.J. Boul, J. Liu, E.T. Mickelson, C.B. Huffman, L.M. Ericson, I.W. Chiang, K.A. Smith, D.T. Colbert, R.H. Hauge, J.L. Margrave, R.E. Smalley, *Chem. Phys. Lett.* 310, 367-372 (1999), the entire teachings of which are incorporated herein by reference.

Nanotubules of the present invention can be "capped", "open-ended", or "closed". "Open-ended" nanotubules have no carbon atoms or functional groups closing off either end of the nanotubule, such that a gas, molecule, or other substance having a diameter less than that of the nanotubule can freely pass from the exterior to the interior of the nanotubule through an end of the nanotubule. Although open-ended nanotubules do not have functional groups closing off an end of the nanotubule, open-ended nanotubules typically have functional groups, such as carboxylate groups, at the ends of the nanotubule. "Closed" nanotubules have graphitic hemispheres at each end of the nanotubule. "Capped" nanotubules are partially or completely closed at one or both ends of the nanotubule by addition of a capping molecule to the end of a nanotubule, such that a gas, molecule, or other substance having a diameter less than that of the nanotubule cannot freely pass from the exterior to the interior of the nanotubule through an end of the nanotubule, and vice versa. A substance, typically in the gaseous state, having a diameter less than that of the nanotubule can more freely pass from the exterior to the interior of the

nanotubule (or vice versa) through an end of the nanotubule once the capping molecule has been cleaved from the end of a molecule, such as by hydrolysis.

Advantageously, the groups which cap the end of a nanotubule are selected so that they are cleavable. Cleavable functional groups include amides, esters, carbonates, carbamates, ureas, acylureas, phosphate esters, phosphonate esters, sulfonate esters, and sulfate esters. Cleavable functional groups are generally reactive in a biological milieu and cleave on a time course relevant to release of nitric oxide or a gas nitric oxide-like activity. Cleavable functional groups are often chosen towards a utility, such that a cleavable functional group intended for pharmaceutical purposes cleaves at a target site.

Typically, a capping molecule is attached to a nanotubule through two functional groups, such that the molecule connects two carbon atoms on the end of a nanotubule. One example of a capped nanotubule of this type is represented schematically below:



The diagram represents a portion at the end of a nanotubule, however, not all bonds are shown. As discussed above, an open-ended nanotubule can have functional groups at its ends. The nanotubule can be capped, for example, by a suitable mono- or difunctional capping reagent. A preferred difunctional reagent is an α,ω-substituted alkyl group (e.g., a C1-C24 alkyl group), which is substituted at one terminus with functional group X and at the other terminus with functional group Y, each of which can react with the functional group(s) at the end of the nanotubule. This is shown schematically above where the functional groups at the end of the nanotubule are carboxylate groups. One skilled in the art can select appropriate combinations of nanotubule functional group and capping reagent; for example, a carboxylate nanotubule functional group is reacted with a capping reagent having amino and/or hydroxyl groups. By connecting two points on the end of a nanotubule, the capping molecule more effectively limits gas exchange between the ambient atmosphere and the interior of the nanotubule. A similar effect is obtained when a monofunctional molecule serves as a capping group. Specific examples of the preparation of nanotubules with capping molecules can be found in Chen, J.; Hamon, M. A.; Hu, H.; Chen, Y.; Rao, A. M.; Eklund, P. C.; Haddon, R. C., *Science*, 282, 95 (1998); Wong, S. S.; Joselevich, E.; Woolley, A. T.; Cheung, C. L.; Lieber, C. M., Nature, 394, 52 (1998); Wong, S. S.; Woolley, A. T.; Joselevich, E.; Cheung, C. L.; Lieber, C. M., *J. Am. Chem. Soc.*, 120, 8557 (1998); Hamon, M. A.; Chen, J.; Hu, H.; Chen, Y.; Itkis, M. E.; Rao, A. M.; Eklund, P. C.; Haddon, R. C., *Adv. Mater.*, 11, 834 (1999); and Ausman, K. D.; Piner, R.; Lourie, O.; Ruoff, R. S.; Korobov, M., *J. Phys. Chem. B*, 104, 8911 (2000), the entire teachings of which are incorporated herein by reference.

Optionally, the nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity are entrained within a polymer. These nanotubules can optionally contain oxygen or other gases as well. Nanotubules that are entrained within a polymer are distributed, preferably homogeneously, throughout the polymer composition. To become entrained within a polymer, nanotubules are typically added to a non-solidified polymer, a solution comprising a polymer, or a solution comprising monomers that are subsequently polymerized.

Polymers with nanotubules entrained therein can be hydrophilic, amphipathic, or hydrophobic, but are preferably hydrophobic. Suitable polymers include teflons (e.g., poly(tetrafluoroethylene)), polylactides, polyurethanes, polyanhydrides, and polyesters. Preferred polymers include copolymers comprising isobutylene and styrene repeat units, such as a styrene-isobutylene-styrene block copolymer. It is to be understood that not every nanotubule entrained within a polymer needs to contain nitric oxide or a gas with nitric oxide-like biological activity in order to be encompassed within the invention.

An article is a three-dimensional object or item having some useful function. An article comprises (e.g., incorporates or is coated with) nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity, or a polymer with such nanotubules entrained therein. The article can be a device for which a useful result can be achieved by nitric oxide release, including a medical device suitable for implantation at a treatment site in a subject.

Articles of the present invention can also serve as exogenous sources of nitric oxide, whereby an aqueous solution is contacted with the article and the aqueous solution is administered to an individual. The aqueous solution and the article can be contacted, such as when the aqueous solution passes through or over the article, or the aqueous solution can be stored in the article for a short term (e.g., minutes or hours) or a long term (e.g., days, weeks, months, or longer). The aqueous solution can be administered or infused orally, intranasally, rectally, subcutaneously, intramuscularly, intravenously, intraurethally, intrauterinely, topically, intrabronchially, or by aerosol or spray. Aqueous solutions, after contacting such articles, can be used as a means of delivering nitric oxide or a gas with nitric oxide-like activity to an individual.

Medical devices of the present invention include devices suitable for implantation in a subject, contact with mucous membranes, or contact with biological fluids. The medical device can deliver nitric oxide to the treatment site in the subject after implantation. In one example, implanting a medical device, such as a stent, in a subject at a treatment site at risk for clot formation can be used to inhibit

or prevent restenosis. Examples of suitable medical devices include medical tubing, catheters, and stents. Medical tubing, as used herein, is tubing suitable for internal use in a mammal or for contact with biological fluids. Stents of the present invention can additionally comprise one or more pharmaceutically active agents. Preferably, stents of the present invention are coated with an antiproliferative, immunosuppressive, antibiotic, and/or antimicrobial pharmaceutically active agent and a nanotubule as described herein.

A "treatment site," as defined herein, is a site where surgery is performed or a medical device is implanted. A "treatment site" additionally includes a site where an aqueous solution is delivered or infused. Also, a "treatment site" includes a site in the body of a subject in which a desirable therapeutic effect can be achieved by contacting the site with nitric oxide or a substance having the activity of nitric oxide. "Treatment sites at risk for clot formation," as defined herein, are sites within the circulatory system where blood clots are at risk of forming, e.g., where there is plaque formation, atherosclerosis, an injury to the blood vessel wall, or an obstruction to blood flow. In particular, the treatment sites are located next to, contiguous with, or within a vein, artery, capillary, or other blood vessel. A "subject" or "individual" refers to a human or an animal such as a veterinary animal (e.g., dogs, cats, and the like) and farm animals (e.g., horses, cows, pigs, and the like).

Treatment sites are found, for example, at sites within the body which develop restenosis, injury or thrombosis as a result of trauma caused by contacting the site with a synthetic material or a medical device. For example, restenosis can develop in blood vessels which have undergone coronary procedures or peripheral procedures with PTCA balloon catheters (e.g. percutaneous transluminal angioplasty). Restenosis is the development of scar-like tissue from about three to six months after the procedure and results in narrowing of the blood vessel. Nitric oxide and gases with the biological activity thereof reduce restenosis by inhibiting platelet deposition and smooth muscle proliferation. Nitric oxide and gases with the biological activity thereof also inhibit thrombosis by inhibiting platelets and can limit injury by serving as an anti-inflammatory agent.

A site in need of treatment with nitric oxide or gases with the biological activity thereof often develops at vascular sites which are in contact with a synthetic material or a medical device. For example, stents are often inserted into blood vessels to prevent restenosis and re-narrowing of a blood vessel after a procedure such as angioplasty. Platelet aggregation resulting in thrombus formation is a complication which can result from the insertion of stents. Nitric oxide is an antiplatelet agent and can consequently be used to lessen the risk of thrombus formation associated with the use of these medical devices. Other examples of medical devices which contact vascular sites and thereby increase the risk of thrombus formation include sheaths for veins and arteries and GORE-TEX surgical prostheses.

The need for treatment with nitric oxide and gases with the biological activity thereof can also develop at non-vascular sites, for example at sites where a useful therapeutic effect can be achieved by reducing an inflammatory response. Examples include the airway, the gastrointestinal tract, bladder, uterus and corpus cavernosum. Thus, the compositions, methods and devices of the present invention can be used to treat respiratory disorders, gastrointestinal disorders, urological dysfunction, impotence, uterine dysfunction and premature labor. NO delivery at a treatment site can also result in smooth muscle relaxation to facilitate insertion of a medical device, for example in procedures such as bronchoscopy, endoscopy, laparoscopy and cystoscopy. Delivery of NO can also be used to prevent cerebral vasospasms post hemorrhage and to treat bladder irritability, urethral strictures and biliary spasms.

The need for treatment with nitric oxide or gases with the biological activity thereof can also arise external to the body in medical devices used to treat bodily fluids temporarily removed from body for treatment, for example blood. Examples include conduit tubes within heart lung machines, tubes of a dialysis apparatus and catheters.

The method of delivering nitric oxide or gases with the biological activity thereof to a treatment site in a subject comprises implanting a medical device which

comprises one or more compounds of the present invention at the treatment site. Nitric oxide or gases with the biological activity thereof can be delivered to bodily fluids, for example blood, by contacting the bodily fluid with a tube or catheter comprising one or more nanotubules of the present invention. Examples of treatment sites in a subject, medical devices suitable for implementation at the treatment sites and medical devices suitable for contacting bodily fluids such as blood are described in the paragraphs hereinabove.

"Implanting a medical device at a treatment site" refers to bringing the medical device into actual physical contact with the treatment site or, in the alternative, bringing the medical device into close enough proximity to the treatment site so that nitric oxide or gases with the biological activity thereof released from the medical device comes into physical contact with the treatment site. A bodily fluid is contacted with a medical device, e.g., a tube or catheter, when, for example, the bodily fluid is temporarily removed from the body for treatment by the medical device, and the coating is an interface between the bodily fluid and the medical device. Examples include the removal of blood for dialysis or by heart lung machines.

Optionally, articles of the present invention are coated with nanotubules or a polymer with nanotubules entrained therein. An article, for example, a medical device such as a stent, tube or catheter, can be coated with one or more compositions of the present invention. In order to form a coating, a solution comprising a composition containing nitric oxide or a gas with nitric oxide-like biological activity is contacted with an article insoluble in the solution. When the composition is insoluble in solution, the composition precipitates from the solution and coats the article. When the composition is soluble in the solution, the article can be dipped into or sprayed with the solution and then dried *in vacuo* or under a stream of an inert gas such as nitrogen or argon, thereby coating the article.

Articles of the present invention also include condoms. Condoms can be designed for use by either males or females. Condoms can be formed from suitable materials, particularly polymers. Suitable materials include latex, rubber, and

polyurethane. The nanotubules can be entrained in the condom, particularly when the condom is comprised of one or more polymers, or can coat the condom.

Articles of the present invention also include pills and capsules comprising a pharmaceutically active agent and a coating or shell comprising one or more nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity. Coated tablets of the invention can be prepared by a method comprising the step of contacting a tablet core comprising a pharmaceutically active agent with a coating solution comprising a solvent, at least one coating agent dissolved or suspended in the solvent, one or more nanotubules, and, optionally, one or more plasticizing agents. Preferably, the solvent is an aqueous solvent, such as water or an aqueous buffer, or a mixed aqueous/organic solvent. Suitable coating agents include beeswax, glyceryl monostearate, shellac, cetyl alcohol, mastic, stearic acid, cellulose, ethyl cellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate polymer, hydroxypropylcellulose, cross-linked sodium carboxymethylcellulose, microcrystalline cellulose, ethylcellulose, methylcellulose, cellulose acetophthalate, methylcellulose acetophthalate, cellulose acetate tetrahydrophalate, cellulose acetopropionate, cellulose trimetallate, cellulose acetate, cellulose butyrate, carboxymethyl starch, starches, starch derivates, polyvinyl acetate, carboxyvinylpolymers, polyvinylalcohol optionally cross-linked with glyoxal, formaldehyde, or glutaraldehyde, cross-linked polyvinylpyrrolidone, poly(methyl vinyl ethers-co-maleic anhydride), neutral copolymers of polymethacrylic acid esters (Eudragit L30D), copolymers of methacrylic acid and methacrylic acid methyl ester (Eudragits), a neutral copolymer of polymethacrylic acid esters containing metallic stearates, potassium methacrylate-divinylbenzene copolymer, acrylic and methacrylic copolymer, methyl methacrylate, methacrylic acid, ethyl acetate latexes, beta-cyclodextrine, dextrine derivatives, mannitol, lactose, sorbitol, xylitol, glucans, scleroglucans, mannans, galactomannans, carrageenan and derivatives thereof, xanthans, alginic acid and derivatives thereof, pectin, amylose, sandarac gum, and mixtures thereof. Suitable plasticizers include polyethylene glycol (PEG 200, PEG 1000), polyoxyethylene glycols, diethyl phthalate, dibutyl phthalate, triacetin, monoglyceride, rape seed oil, olive oil, sesame

oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, hydrogenated castor oil, fatty acids, substituted glycerides and triglycerides, glycerol, D-sorbitol, sucrose, mannitol, fructose, sugar alcohol, isomerized sugars, and propylene glycol. Typically, the tablet core is contacted with the coating solution until the weight of the tablet core has increased by an amount ranging from about 1% to about 20%, indicating the deposition of a suitable coating on the tablet core to form a coated tablet.

Capsules typically comprise a shell and a solid or liquid core comprising a pharmaceutically active agent. The shell can be hard or soft and is typically comprised of a suitable solid coating material, such as gelatin, agar, sodium alginate, pectin, carageenan, carboxymethyl cellulose, gelant gum, poly(sodium acrylate), poly(sodium methacrylate), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, acrylic acid polymer, methacrylic acid copolymers, ethyl acrylate-methyl methacrylate copolymers, and mixtures thereof; one or more nanotubules; and a plasticizer or another suitable material to modify the properties of the shell, such as those named above. The capsules can contain the pharmaceutically active agents in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers such as gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens such as e.g., Tween 20 and Tween 80 (ICI Speciality Chemicals)); polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium

aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (block copolymers of ethylene oxide and propylene oxide); poloxamines (a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine), dialkylesters of sodium sulfosuccinic acid (e.g., a dioctyl ester of sodium sulfosuccinic acid); sodium lauryl sulfate; alkyl aryl polyether sulfonate; a mixture of sucrose stearate and sucrose distearate; p-isononylphenoxypoly-(glycidol); decanoyl-N-methylglucamide; n-decyl-beta-D-glucopyranoside; n-decyl-beta-D-maltopyranoside; n-dodecyl-beta-D-glucopyranoside; n-dodecyl-beta-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-beta-D-glucopyranoside; n-heptyl-beta-D-thioglucoside; n-hexyl-beta-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl-beta-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-beta-D-glucopyranoside; and octyl-beta-D-thioglucopyranoside. In hard capsules, the solid core can be comprised of particles; each particle can have a coating (e.g., with a coating suitable for tablets, as described above) comprising one or more nanotubules of the present invention. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added.

Articles other than pills and capsules can also comprise a pharmaceutically active agent. Suitable pharmaceutically active agents for use in the present invention include antibiotics, antimicrobials, antiproliferative agents, immunosuppressive agents, anti-inflammatory agents and COX-2 inhibitors. Examples of antibiotics and antimicrobials include streptomycin, rifamycin, amphotericin B, griseofulvin, penicillin, cephalothin, cefazolin, chloramphenicol, fluconazole, clindamycin, erythromycin, bacitracin, vancomycin, ciprofloxacin, tetracycline, and fusidic acid. Examples of antiproliferative and immunosuppressive agents include corticosteroids, cyclosporine, tacrolimus, interferons (e.g., IFNα, IFNβ, IFNγ), mycophenolate mofetil, 15-deoxyspergualin, thalidomide, azathioprene, cyclophosphamide, azacitidine, cytarabine, fluorouracil, mercaptoprine,

methotrexate, thioguanine, bleomycin, etoposide, teniposide, vincristine, vinblastine, busulfan, mechlorethamine, melphalan, thiotepa, dactinomycin, daunorubicin, doxorubicin, plicamycin, mitomycin, cisplatin, and nitrosoureas. Preferred antiproliferative and immunosuppressive agents include paclitaxel and rapamycin. Examples of anti-inflammatory agents and COX-2 inhibitors include aspirin, acetominaphen, and non-steroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen, nabumetone, apazone, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, indomethacin, keoprofen, ketorolac, meclofenamate, oxaprozin, piroxicam, sulindac, tolmetin, rofecoxib, celecoxib, valdecoxib, meloxicam).

As used herein, a "surfactant" is an agent which preferentially absorbs to an interface between two immiscible phases, such as the interface between water and an organic polymer solution, a water/air interface or organic solvent/air interface. Surfactants generally possess a hydrophilic moiety and a lipophilic moiety. Suitable surfactants include but are not limited to phospholipids such as 1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine, 1,2-Distearoyl-*sn*-glycero-3-phosphocholine, phosphatidyl ethanolamine, phosphatidylcholine, phosphatidylethnolamine, phosphatydilinositol, phosphatidylserine, and phosphatidylglycerol; hexadecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; glycocholate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate (Span 85); tyloxapol; alcohol ethyoxylates; alkylphenol ethoxylates; fatty amine oxides; alkalonamides; ethylene oxide/propylene oxide block copolymers; poly-oxyalkylene glycols; polyoxypropylene glycol monoalkylethers; poly-(oxyethylene oxypropylene) glycol monoalkylethers; imidazolines; betaines; alkylbenzene sulfonic acid; sodium lauryl ether sulfate; alpha olefin sulfonates; phosphate esters; and sodium sulfosuccinates.

Perfluorocarbons (PFCs) are hydrocarbons with all of the hydrogen atoms replaced by fluorine, although one to five of the fluorine atoms can be another halogen. Perfluorocarbons includes perfluorodecaline, perfluorotripropylamine, perfluorooctyl bromide, and perfluorodichlorooctane.

Cyclodextrins include α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin. Cyclodextrins can be converted to polythiolated cyclodextrins, for example, by the methods disclosed in Gaddell and Defaye, *Angew. Chem. Int. Ed. Engl.* 30: 78, 1991 and Rojas *et al.*, *J. Am. Chem. Soc.* 117: 336, 1995, the teachings of which are incorporated herein by reference. An excess of thiolating reagent can be used to form perthiolated cyclodextrins, whereby all primary alcohols are converted to thiol groups.

In the preparation of nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity, the nanotubules are preferably contacted with a gas consisting essentially of nitric oxide or a gas with nitric oxide-like biological activity. The nanotubules are in contact with the gas for a sufficient amount of time to obtain a nanotubule with the desired weight percent content of the gas. More preferably, the nanotubules are contacted with an oxygen-free inert gas or combination of inert gases prior to contacting the nanotubules with nitric oxide. Examples of inert gases include nitrogen, argon, helium, and neon.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims. The invention will now be further and specifically described by the following non-limiting Examples.

EXAMPLES

Preparation and assays of NO-loaded carbon nanotubes (CNs)

Example 1 - Loading and heat assay

A 125 mL bottle with a poly(tetrafluoroethylene)-faced (PTFE-faced), silicone rubber open-top cap was filled with glass vials and glass wool to an extent that a 2 mL vial could be placed very nearly at the top of the bottle. Single-walled

carbon nanotublules (hereinafter "CN", Aldrich 519308, CarboLex AP-grade, 17.3 mg) were placed in a 2 mL vial, which was put into the 125 mL bottle. By means of a 6 inch needle, argon gas was blown slowly through the bottom of the 125 mL bottle for 25 minutes, with egress through a hypodermic needle at the top. By the same process, NO gas was blown through the bottom of the 125 mL bottle for 20 minutes; the NO gas was first blown through granular KOH and a water bubbler to remove trace NO_2. The sealed bottle was stored in the dark at 25°C for 7.5 hours. By means of a 6 inch needle, nitrogen gas was blown rapidly through the bottom of the 125 mL bottle for 13 minutes, with egress through a hypodermic needle at the top. The bottle was opened to atmosphere, and the 2 mL vial was removed. Deionized water (1000 µL) was added to the vial, the head space was filled with oxygen, and the vial was capped with a PTFE-faced, silicone rubber open-top cap. The cap was secured to the vial with autoclave tape, and the vial was stored at 80-90°C for 14 hours. The vial was cooled to 25°C. A 7.5 µL aliquot of the water was found to contain 61.7 nmol nitrogen oxides (NO_x) by chemiluminescence, corresponding to 476 nmol NO per milligram of CN, roughly 1.4% loading (w/w). A control sample of CN (33.7 mg) that was not treated with NO gas had no measurable NO_x. A control sample of pure carbon (Aldrich 484164, glassy, spherical powder, 2-12 micron, 66.2 mg) that was treated with NO as described above had no measurable NO_x.

Example 2 - Bioassay (rabbit aortal assay)

The capacity of a compound or composition to cause relaxation of vascular smooth muscle, measured by the degree and duration of vasodilation resulting from exposure of a blood vessel to the compound, is a measure of its ability to deliver NO *in vivo*. Methods reported in Jia, L., *et al., Nature,* 380:221-226, 1996; Stamler, J.S., *et al., Science,* 276:2034-2037, 1997; Stamler *et al., Proc. Natl. Acad. Sci. USA 89:*444, 1992; Osborne *et al., J. Clin. Invest. 83:*465, 1989; and the chapter by Furchgott in *Methods in Nitric Oxide Research*, edited by Feelisch and Stamler, John Wiley & Sons (1996), were used to measure vascular smooth muscle contraction.

By the means described in Example 1, NO-loaded CNs were prepared from 19.4 mg CN, with, sequentially, 25 minutes of Ar gas flow, 35 minutes of NO gas flow, and 16 hours of storage under NO. NO was removed from the 125 mL bottle by flushing with Ar gas for 25 minutes; the NO-loaded CNs were then stored under Ar for 30 hours.

New Zealand White female rabbits weighing 3-4 kg were anesthetized with sodium pentobarbital (30 mg/kg). Descending thoracic aorta were isolated, the vessels were cleaned of adherent tissue, and the endothelium was removed by gentle rubbing with a cotton-tipped applicator inserted into the lumen. The vessels were cut into 5-mm rings and mounted on stirrups in 20 mL organ baths. The rings were suspended under a resting force of 1 g in 7 ml of oxygenated Kreb's buffer (pH 7.5) at 37°C and allowed to equilibrate for one hour. Isometric contractions were measured on a Model 7 oscillograph recorder connected to transducers (model TO3C, Grass Instruments, Quincy, MA). Fresh Krebs solution was added to the bath periodically during the equilibration period and after each test response. Sustained contractions were induced with 7 μM norepinephrine prior to the addition of the test compound. The assay demonstrated bioactivity; very small (approximately 160 μg) additions of NO-loaded CN to the aortal rings showed both short- and long-term relaxation. Similar amounts of CN not treated with nitric oxide had little or no activity.

Example 3 - NO release from NO-loaded CNs into Phosphate-Buffered Saline

By the means described in Example 1, two samples of NO-loaded CNs (CN-NO) were prepared:

(1) From 19.4 mg CN, with, sequentially, 25 minutes of Ar gas flow, 35 minutes of NO gas flow, and 16 hours of storage under NO. NO was removed from the 125 mL bottle by flushing with Ar gas for 25 minutes; the CN-NO was stored under Ar for 30 hours. The CN-NO was stored in a 2 mL vial under ambient atmosphere for 3 days.

(2) From 23.1 mg CN, with, sequentially, 25 minutes of Ar gas flow, 35 minutes of NO gas flow, and 20 hours of storage under NO. NO was removed from the 125 mL bottle by flushing with Ar gas for 25 minutes; the CN-NO was stored under Ar for 20 hours. The CN-NO was stored in a 2 mL vial under ambient atmosphere for 2 days.

Small samples (6.0 mg of sample (1), 7.6 mg of sample (2)) were weighed into 2 mL screw-cap vials, phosphate-buffered saline (PBS, 1000 µL, 25°C) was added at time $t = 0$, vials were stored at 37°C, and aliquots (25 µL) were analyzed at time points for NO_x content. Both samples showed release beyond the first day (Figure 1).

Example 4 - NO release from CN-NO entrained in SIBS (Styrene-Isobutylene-Styrene Copolymer) into PBS

By the means described in Example 1, two samples of CN-NO were prepared:

(1) From 19.4 mg CN, with, sequentially, 25 minutes of Ar gas flow, 35 minutes of NO gas flow, and 16 hours of storage under NO. NO was removed from the 125 mL bottle by flushing with Ar gas for 25 minutes; the CN-NO was stored under Ar for 30 hours. The CN-NO was stored in a 2 mL vial under ambient atmosphere for 3 days.

(2) From 23.1 mg CN, with, sequentially, 25 minutes of Ar gas flow, 35 minutes of NO gas flow, and 20 hours of storage under NO. NO was removed from the 125 mL bottle by flushing with Ar gas for 25 minutes; the CN-NO was stored under Ar for 20 hours. The CN-NO was stored in a 2 mL vial under ambient atmosphere for 2 days.

Small samples (4.8 mg of sample (1), 8.3 mg of sample (2)) were weighed into 2 mL screw-cap vials. A stock solution of SIBS polymer in dichloromethane (5.5058 g in 100 mL) was prepared and bubbled with argon for 15 min; 1 mL was added to each vial (approximately 52.2 mg SIBS). Solvent was removed by blowing

nitrogen through each vial (approxmately 5 minutes) to give CN-NO entrained in SIBS. Samples were stored in the dark at 25°C for 24 hours. PBS (1500 µL, 37°C) was added at time $t = 0$, vials were stored at 37°C, and aliquots (25 µL) were analyzed (described earlier) at time points for NO_x content. Both samples showed sustained release beyond the first day (Figure 2).

Example 5 -Loading of CN entrained in SIBS polymer

Single-walled CNs (Aldrich 519308, CarboLex AP-grade, 16.0 mg) were placed in a 2-mL vial. A stock solution of SIBS polymer in dichloromethane (5.5058 g in 100 mL) was prepared and bubbled with argon for 15 minutes; 1 mL was added to the vial (approximately 52.2 mg SIBS). Solvent was removed by blowing nitrogen through the vial (approximately 5 minutes) to give CN entrained in SIBS. The vial was treated with NO as described in Example 1, with 25 minutes of Ar gas flow, 31 minutes of NO gas flow, and 24 hours of storage under NO. NO was removed from the 125 mL bottle by flushing with Ar gas for 36 minutes. The vial containing CN-NO in SIBS was briefly exposed to ambient atmosphere while it was removed from the 125 mL bottle; the vial was capped for 4.5 hours. Deionized water (1000 µL) was added to the vial, the head space was filled with oxygen, and the vial was capped with a PTFE-faced, silicone rubber open-top cap. The cap was secured to the vial with autoclave tape, and the vial was stored at 80-90°C for 12 hours. The vial was cooled to 25°C. After 6 hours from the time of cooling, a 10-µL aliquot of the water was found to contain 18.4 nmol NO_x, corresponding to 115 nmol NO per milligram of CN. After 144 hours from the time of cooling, a 10-µL aliquot of the water was found to contain 22.6 nmol NO_x, corresponding to 141 nmol NO per milligram of CN.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A composition comprising a compound that non-covalently binds nitric oxide or a gas with nitric oxide-like biological activity and nitric oxide or a gas with nitric oxide-like activity non-covalently bound to said compound.

2. A nanotubule, wherein said nanotubule contains nitric oxide or a gas with nitric oxide-like biological activity and wherein the interior of said nanotubule is substantially free of oxygen.

3. The nanotubule of Claim 2, wherein the nanotubule contains a gas with nitric oxide-like biological activity.

4. The nanotubule of Claim 3, wherein the gas with nitric oxide-like biological activity is nitrogen dioxide, dinitrogen trioxide, an alkyl nitrite, or ethyl nitrite.

5. The nanotubule of Claim 2, wherein the nanotubule contains nitric oxide.

6. The nanotubule of Claim 2, wherein the nanotubule has a diameter between about 1 nm about 50 nm and a length between about 10 nm and about 100 µm.

7. A nanotubule, wherein said nanotubule is functionalized with a functional group and contains nitric oxide or a gas with nitric oxide-like biological activity.

8. The nanotubule of Claim 7, wherein the nanotubule contains nitric oxide.

9. The nanotubule of Claim 8, wherein said nanotubule is functionalized with fluoride, an alcohol, an amine, an alkyl group, or a combination thereof.

10. A nanotubule, wherein the ends of said nanotubule are functionalized with one or more capping molecules and wherein said nanotubule contains nitric oxide or a gas with nitric oxide-like biological activity.

11. The nanotubule of Claim 10, wherein said capping molecule is attached to a nanotubule by one or more amide, ester, carbonate, carbamate, urea, acylurea, phosphate ester, phosphonate ester, sulfonate ester, or sulfate ester moieties, or a combination thereof.

12. The nanotubule of Claim 2, wherein the nanotubule is single-walled.

13. The nanotubule of Claim 2, wherein the nanotubule is multi-walled.

14. The nanotubule of Claim 2, wherein the nanotubule is open-ended.

15. The nanotubule of Claim 2, wherein nitric oxide or the gas with nitric oxide-like biological activity contained by the nanotubule comprises 0.5-10 weight percent of said nanotubule.

16. The nanotubule of Claim 15, wherein nitric gas or the gas with nitric oxide-like biological activity contained by the nanotubule comprises 0.5-6 weight percent of the nanotubule.

17. An article comprising one or more nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity.

18. The article of Claim 17, wherein said article is a bag containing intravenous fluid, a syringe, or medical tubing.

19. The article of Claim 17, wherein the nanotubules contain nitric oxide.

20. The article of Claim 19, further comprising a polymer with the nanotubules entrained therein.

21. The article of Claim 20, wherein the polymer coats the article.

22. The article of Claim 19, wherein the polymer is a copolymer comprising isobutylene and styrene repeat units.

23. The article of Claim 19, wherein the polymer is poly(tetrafluoroethylene).

24. The article of Claim 19, further comprising a pharmaceutically active agent.

25. The article of Claim 19, wherein the article is a condom.

26. A pill or capsule comprising a pharmaceutically active agent and a coating comprising one or more nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity.

27. The pill or capsule of Claim 26, wherein the pharmaceutically active agent is an antiproliferative agent.

28. The pill or capsule of Claim 27, wherein the antiproliferative agent is paclitaxel or rapamycin.

29. The pill or capsule of Claim 26, wherein the pharmaceutically active agent is a COX-2 inhibitor.

30. The pill or capsule of Claim 29, wherein the COX-2 inhibitor is aspirin or a non-steroidal anti-inflammatory drug.

31. A medical device suitable for implantation in a subject, for contact with mucous membranes, or for contact with a biological fluid, wherein said device comprises one or more nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity.

32. The medical device of Claim 31, wherein said device is medical tubing or a stent.

33. The medical device of Claim 32, wherein said device is a stent comprising an antiproliferative or immunosuppressive pharmaceutically active agent.

34. The medical device of Claim 33, wherein the pharmaceutically active agent is paclitaxel or rapamycin.

35. A method of inhibiting restenosis, comprising implanting a stent comprising one or more nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity.

36. The method of Claim 35, wherein the nanotubules contain nitric oxide.

37. The method of Claim 36, wherein the stent is coated with a pharmaceutically active agent having antiproliferative or immunosuppressive activity.

38. The method of Claim 37, wherein the pharmaceutically active agent is paclitaxel or rapamycin.

39. A method of delivering nitric oxide to a treatment site by implanting a medical device comprising one or more nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity.

40. The method of Claim 39, wherein the nanotubules contain nitric oxide.

41. The method of Claim 40, wherein the treatment site is at risk for clot formation.

42. A method of preparing nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity, comprising the step of contacting said

nanotubules with nitric oxide or a gas with nitric oxide-like biological activity, wherein nitric oxide or the gas with nitric oxide-like biological activity is substantially free of oxygen.

43. The method of Claim 42, wherein the nanotubules are contacted with a gas consisting essentially of nitric oxide.

44. The method of Claim 43, further comprising contacting the nanotubules with an oxygen-free inert gas or combination of inert gases prior to contacting the nanotubules with nitric oxide.

45. A polymer entrained with nanotubules, wherein said nanotubules contain nitric oxide or a gas with nitric oxide-like biological properties.

46. The polymer of Claim 45, wherein said nanotubules contain nitric oxide.

47. The polymer of Claim 46, wherein said polymer is a copolymer comprising isobutylene and polystyrene repeat units.

48. A composition comprising a polymer and nanotubules entrained in the polymer, wherein said nanotubules contain nitric oxide or a gas with nitric oxide-like biological activity.

49. The composition of Claim 48, wherein the nanotubules contain nitric oxide.

50. A method of administering nitric oxide or a gas with nitric oxide-like properties to an individual, comprising the step of contacting an aqueous

solution with an article comprising one or more nanotubules containing nitric oxide or a gas with nitric oxide-like biological activity and administering said aqueous solution to said individual.

51. The method of Claim 50, wherein the article is a bag containing intravenous fluid, a syringe, or medically-suitable tubing.

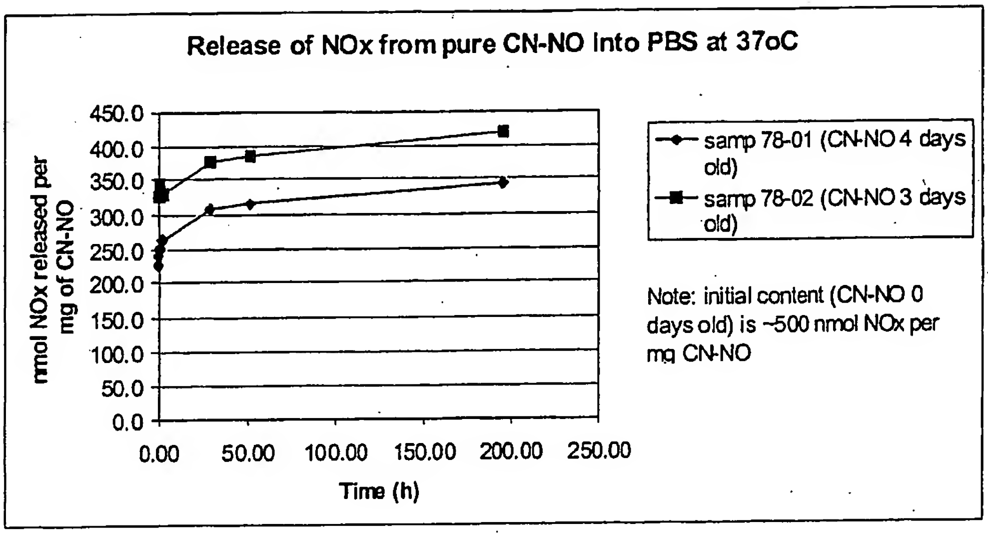

Release of NOx from pure CN-NO into PBS at 37oC
nmol NOx released per mg of CN-NO
450.0
400.0
350.0
300.0
250.0
200.0
150.0
100.0
50.0
0.0
0.00
50.00
100.00
150.00
200.00
250.00
Time (h)
samp 78-01 (CN-NO 4 days old)
samp 78-02 (CN-NO 3 days old)
Note: initial content (CN-NO 0 days old) is ~500 nmol NOx per mg CN-NO

Figure 1

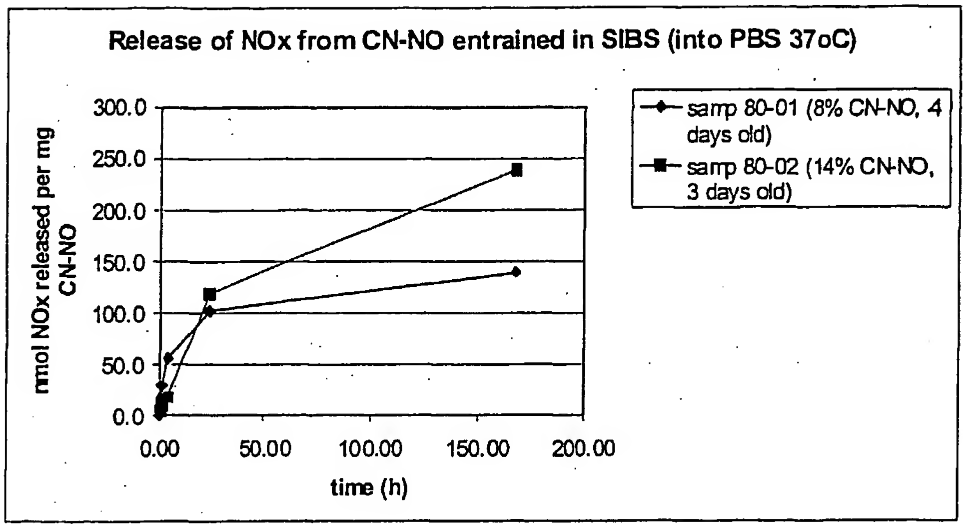

Release of NOx from CN-NO entrained in SIBS (into PBS 37oC)
nmol NOx released per mg CN-NO
300.0
250.0
200.0
150.0
100.0
50.0
0.0
0.00
50.00
100.00
150.00
200.00
time (h)
samp 80-01 (8% CN-NO, 4 days old)
samp 80-02 (14% CN-NO, 3 days old)

Figure 2

INTERNATIONAL SEARCH REPORT

In[redacted]tional Application No
PCT/US 03/13289

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L29/12 A61L29/14 A61L31/12 A61L31/14 A61L33/02
A61L33/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 68158 A (ORBUS MEDICAL TECHNOLOGIES INC) 20 September 2001 (2001-09-20) page 11, line 30 -page 13, line 11 ---	1-51
Y	WO 99 32184 A (CORDIS CORP ;LEONE JAMES E (US); NARAYANAN PALLASSANA V (US)) 1 July 1999 (1999-07-01) page 8, line 1 - line 13 ---	1-51
Y	WO 00 44357 A (MAX DELBRUECK CENTRUM ;LEONHARDT HEINRICH (DE)) 3 August 2000 (2000-08-03) page 3, paragraph 1 - paragraph 5 ---	1-51
Y	EP 1 054 036 A (FINA RESEARCH) 22 November 2000 (2000-11-22) page 2, line 52 - line 58 ---	1-51
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2003	23/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giménez Miralles, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 67296 A (UNIV DUKE) 29 December 1999 (1999-12-29) the whole document ---	1-51
Y	WO 98 05689 A (UNIV DUKE) 12 February 1998 (1998-02-12) the whole document -----	1-51

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 35-41, 50 and 51 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 35-41,50,51

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Claims Nos.: 1 partially

Present claim 1 relates to an extremely large number of possible compounds and compositions ("a composition comprising a compound that non-covalently binds nitric oxide" or "nitric oxide non-covalently bound to said compound"). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/compositions claimed, namely carbon nanotubules or nanotubes of fullerene type, wherein nitric oxide is loaded/adsorbed into said nanotubules, within the meaning of claim 2. The speculative statement in the description "suitable compositions include surfactants, perfluorocarbons, polythiolated cyclodextrins, and cyclodextrins" (see page 3, lines 2-3) cannot be considered as sufficient disclosure for the subject-matter as claimed in present claim 1. Therefore, in the present case, claim 1 so lacks support, and/or the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to said carbon nanotubules containing nitric oxide within the meaning of claim 2, and polymeric materials entraining said carbon nanotubules within the meaning of claims 45-49.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/13289

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 35-41,50,51
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1 partially
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[redacted]ional Application No

PCT/US 03/13289

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0168158 A	20-09-2001	AU 4573401 A	24-09-2001
		CA 2400319 A1	20-09-2001
		CN 1418115 T	14-05-2003
		EP 1263484 A1	11-12-2002
		WO 0168158 A1	20-09-2001
		US 2002049495 A1	25-04-2002
WO 9932184 A	01-07-1999	AU 1922799 A	12-07-1999
		EP 1039944 A1	04-10-2000
		WO 9932184 A1	01-07-1999
		US 6468244 B1	22-10-2002
WO 0044357 A	03-08-2000	DE 19903385 A1	03-08-2000
		WO 0044357 A2	03-08-2000
EP 1054036 A	22-11-2000	EP 1054036 A1	22-11-2000
		AU 4565900 A	05-12-2000
		WO 0069958 A1	23-11-2000
		EP 1181331 A1	27-02-2002
		JP 2002544356 T	24-12-2002
		US 6331265 B1	18-12-2001
WO 9967296 A	29-12-1999	US 6232434 B1	15-05-2001
		AU 4692999 A	10-01-2000
		CA 2336138 A1	29-12-1999
		EP 1093468 A1	25-04-2001
		JP 2002518557 T	25-06-2002
		WO 9967296 A1	29-12-1999
		US 2003078365 A1	24-04-2003
		US 2001020083 A1	06-09-2001
WO 9805689 A	12-02-1998	US 5770645 A	23-06-1998
		AT 219108 T	15-06-2002
		AU 714972 B2	13-01-2000
		AU 3967797 A	25-02-1998
		DE 69713335 D1	18-07-2002
		DE 69713335 T2	13-02-2003
		EP 0914348 A1	12-05-1999
		JP 2001524991 T	04-12-2001
		KR 2000029774 A	25-05-2000
		NZ 334221 A	29-11-1999
		WO 9805689 A1	12-02-1998
		US 6232434 B1	15-05-2001
		US 2003078365 A1	24-04-2003
		US 2001020083 A1	06-09-2001